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MONOGRAPHS ON PHYSIOLOGY

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THE SECRETION OF THE URINE

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BY

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EDITOR'S PREFACE.

In no science is the advance at any one time general. Some sections of the line are pushed forward while other parts may remain for years with little movement, until in their turn they are enabled to progress in consequence of the support afforded by the advance of the adjacent sections. The increasing number of series of monographs in different sciences is a recognition of this fact, as well as of the concentration of interest which characterizes this age of specialization.

In the present series it is intended to set out the progress of physiology in those chapters in which the forward movement is the most pronounced. Each monograph will contain an account of our knowledge of some particular branch of physiology, written by one who has himself contributed in greater or less degree to the attainment of our present position. It is hoped that by securing the help of men who are actively engaged in the advance of the subject the outlook of each monograph will be forwards rather than backwards. An exhaustive account of previous writings on the subject concerned is not aimed at, but rather an appreciation of what is worth retaining in past work, so far as this is suggestive of the paths along which future research may be fruitful of results. The more valuable the monographs in inspiring the work of others, the greater will be the success of the series.

ERNEST H. STARLING.

TO COLONEL STARLING, M.D., F.R.S., ETC.,

BRITISH EXPEDITIONARY FORCE.

MY DEAR STARLING,

I have now completed the task which you allotted me in your capacity as editor of this series, and which I have found more burdensome than I expected. The growth in the literature on the kidney has been extraordinary since the time when you and I began to work on it, and this increase in bulk has not gone along with an improvement of quality, but rather the reverse. No other organ of the body has suffered so much from poor work as the kidney, and in no other region of physiology does so much base coin pass as legal tender. It was therefore necessary to sift thoroughly this mass of printed matter of over 6000 pages, and I have read it carefully and, as far as might be, sympathetically, though I must confess that my patience has been sorely tried by some papers in which the depth bore no proportion to the length. It soon became obvious that if each writer were to be dealt with faithfully, this would be, not a monograph, but a series of volumes, and the whole trend of the argument would be lost in a tangle of discussions. I have therefore had to dismiss very shortly some papers which were obviously of low value, while others, which seemed equally inconclusive but which have obtained a wider currency, required more consideration. The more important views have been adequately presented, I trust, though the space given them has been curtailed by the necessity

of dealing with others. And as my criticism had to be brief, it may sometimes appear more severe than I designed; anyone who may feel himself aggrieved by it may find some consolation in the pages in which your earlier papers and my own are discussed, where he will find that they also do not pass through the ordeal unscathed.

It is often complained that the physiology of the kidney given in the textbooks is made up of a wrangle between the two great views of its activity; on the other hand, it may be argued that the many isolated observations need to be correlated with each other, and this can only be done by welding them with some definite view of renal function. I have not avoided the controversy, but I have at any rate given the ascertained facts apart from the discussion, so that they at least may remain, whatever theory of kidney activity may survive. The different views are presented, and one is advocated which differs in some respects from any that has been accepted hitherto, and which embraces some of the features of each of its precursors. Since it has been developed gradually from the work of many, it would not be fair to attach to it the name of any one investigator, and I have therefore called it "the modern view"; it has not been treated in detail previously. It is based largely on physical chemistry as well as on the direct observations of physiologists, and it appears to conflict with no ascertained fact in physiology, while it gives an intelligible connection between almost all those that have been established; above all, it is capable of expansion. It has been a special pleasure in working out this view to find that many observations which have been held to be opposed to any such physical correlation really fall into place easily when looked at from the proper angle. I do not flatter myself that this treatise attains finality in regard to the secretion of the

urine; that is impossible at the present time. If it serves as an advanced post from which others may issue against the remaining ramparts of vitalism, its purpose will be attained.

You will probably complain that instead of presenting the facts and following them to the theoretical principle to which they point, I have first stated the theory and then discussed how far each set of observations can be brought into accord with it. I acknowledge the superiority of the first method, but I feared that it was impossible to follow it. For the facts are so multitudinous that unless the student were first given some general scheme on which he could arrange them, he would be lost in detail and might fail to appreciate where the path was leading. Here, even more than elsewhere, I should have been glad to have the advantage of your advice and experience, had your other duties allowed you to play the part of editor and critic more adequately.

I have not felt able to adventure on the difficult country of renal pathology, but some points which have arisen from the consideration of the normal function and which seem to have been neglected by the pathologists, are embodied in the two last chapters; these, of course, make no claim to be exhaustive.

The bibliography is, I hope, nearly complete. References to it in the text are made in part by the date of publication, in part by the number of the paper in the bibliography. I trust that when you have leisure to examine this monograph, you may appreciate the difficulties and excuse the shortcomings.

Yours,

A. R. C.

LONDON, 1917.

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CHAPTER I.

ANATOMY AND HISTOLOGY OF THE KIDNEY.

The tubule—the vessels—number and dimensions of the secretory units—changes during activity—the argument from anatomy—renal nerves and their function—splanchnic and vagus—direct excitation—reflex excitation—the denervated kidney—the central nervous system and secretion.

THE kidney is frequently classed along with the typical secreting glands, but this is not justified either by the history of its development or from its histological characters, which are without analogy in other organs. Developmentally, it is mainly derived from the surface of the cœlum, and is thus a mesodermal structure, while the ordinary glands originate in outgrowths from the surface of the gut and are endodermal, or from the surface of the body and are epidermal in origin.

This fundamental distinction in character is further shown in the histology of the adult organ. The kidney is built up of a large number of units, each of which is formed of a long unbranched tube closed at one end and running a devious route through the cortex and medulla to terminate with many of its fellows in a collecting tubule which opens into the pelvis of the kidney. The collecting tubule does not appear to be concerned in the actual formation of the urine, but merely carries the fluid from the secretory cells to the pelvis and ureter.

The tubule (Fig. 1) which determines the constituents of the urine takes its origin in Bowman's capsule, which may be conceived as a hollow sphere of very delicate epithelium, one side of which is invaginated by a closely twining nodule of capillaries and arterioles, until the cavity is almost entirely obliterated. The capsule along with its capillaries is known as the Malpighian body. The *capsule* opens by a narrow neck into the tubule proper, which doubles and twists (*proximal convoluted tubule*) in the

neighbourhood of the capsule, and then issues in a straight length

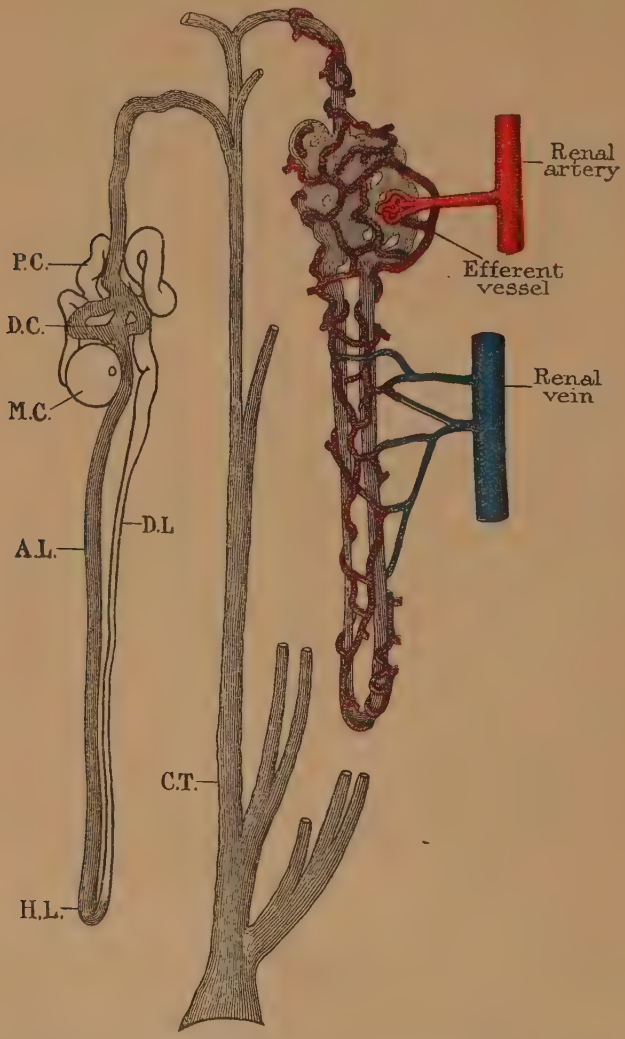

FIG. 1.—On the left the tubule is drawn after a diagram of G. C. Huber's. The tubule is outlined from the capsule to the loop of Henle and is shaded from that point to the end of the collecting tubule. On the right a diagram of the circulation is added : M.C., Malpighian corpuscle ; P.C., proximal convoluted tubule ; D.L., descending limb ; H.L., loop of Henle ; A.L., ascending limb ; D.C., distal convoluted tubule ; C.T., collecting tubule.

directed towards the pelvis of the kidney. After running for some distance through the medulla, it doubles back (*Loop of*

Henle) to the neighbourhood of the capsule again in a straight course, and passing through a second though shorter series of convolutions (*distal convoluted tubule*) ends in the collecting tubule.

The capsule (Fig. 2) is lined by flattened epithelial cells which are especially thin over the nodules of capillaries, and which are supported by a delicate basement membrane. In some animals the cells become more cubical as the opening into the tubule is

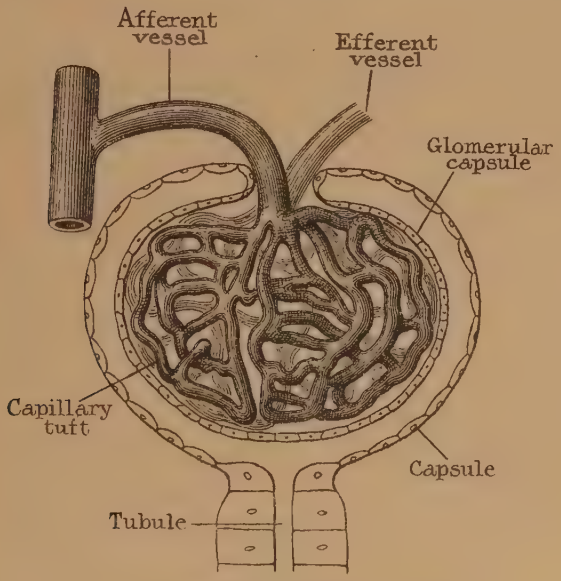

FIG. 2.—Diagram of Malpighian corpuscle.

approached, thus forming a transition to the characteristic high epithelium of the convoluted tubules.

The wall of the tubule proper is formed by epithelial cells of three different types (Fig. 3). The proximal convoluted tubule and the upper part of the descending limb of the loop of Henle are lined by high cells standing on a basement membrane and showing marked striations in their outer zone. These striations can be resolved into rows of granules, which run towards the lumen, becoming less distinct as they approach it, and terminating in very fine granules, which appear to stand in close relation to the prominent striated border which forms the internal border of the cell. Suzuki divides this portion of the tubule into three or four

distinct parts, according to the character of the granulation and the reaction to certain poisons.

The narrow portion of the descending limb of Henle's loop is lined with epithelium of a thin pavement type, with rather large bulging nuclei. The narrowness of this portion of the tubule is due to the thinness of the wall, the lumen being as wide as elsewhere. This part of the tubule shows more variation in length than the others. The lowest part of the descending limb and the loop itself are lined by short columnar cells with an outer finely striated dark zone and an inner lighter one and without a striated free border. This type continues with little further variation until the collecting tubule is reached; the second convoluted tubule resembles the proximal one in character, except in possessing no striated border, and perhaps in failing to stain so readily to

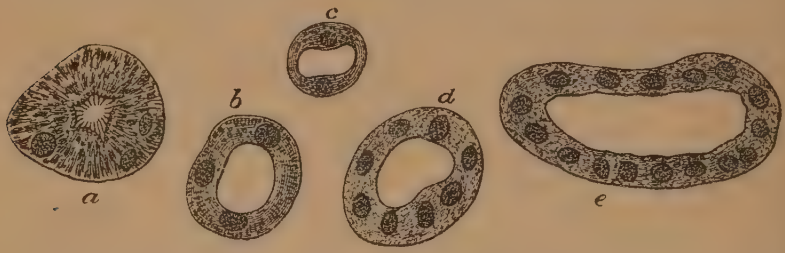

FIG. 3.—Cross-sections of the tubule at different levels: *a*, proximal convoluted; *b*, upper part of descending limb; *c*, thin part of descending limb; *d*, ascending limb; *e*, collecting tubule.

carmine (Suzuki), though others have not observed the latter point of difference. The epithelium throughout the tubule and capsule rests on a fine basement membrane and is supported by reticular tissue in which lie the abundant blood and lymph vessels and nerves.

The tubules in the lower vertebrates resemble in general features those of the mammals. The turtle's kidney differs in the shortness of the tubule, in which the loop is absent or very short, though part of the tubule is lined with low epithelium, corresponding to that of the thin limb of the mammalian loop (Huber). In the frog the mesonephros survives in the adult, no true kidney corresponding to the mammalian organ being developed; the glomerulus is very small, and there is no loop of Henle, but the same types of epithelium may be recognized in the tubule as in the mammal (180). The neck joining the capsule to the convoluted tubule is lined by ciliated epithelium.

The vascular supply of each secretory unit is no less remarkable than the course of the tubules. The arteries radiate through the medulla to the cortex and give off a series of side branches (afferent vessels), each of which after a short course breaks up into a small capillary nodule (glomerulus) which is enclosed in Bowman's capsule ; the epithelium of the capsule is reflected closely over the glomerulus. The capillaries collect into an efferent vessel which is slightly narrower than the afferent artery, and this again breaks into a series of capillaries on the walls of the tubules and forms their only blood supply. This second set of capillaries ends in veins which coalesce to form the renal vein.

The blood thus flows first through the glomerulus supplying the capsule of Bowman and then is distributed to the tubules, including the loop of Henle. The kidney presents within itself the same double capillary arrangement as occurs in the portal system, the glomerulus corresponding to the vessels of the alimentary tract and the second series of capillaries on the tubules to the capillaries of the liver. It has been stated that the tubules also receive arterial blood directly by branches from the main trunks, but the careful researches of Huber (1907) and Gerard (1911) have failed to detect any such arrangement, and it now seems established that practically the whole of the blood supplied to the tubules first passes through the capillaries of the glomerulus.

The kidney is made up of a large number of these units, consisting of glomerulus, capsule, and tubule, with the final collecting tubules. The number of units in each kidney has been counted in the cat by Miller and Carlton (1895), who found 16,000. Brodie (1914) found 142,000 in the kidney (34·5 gm.) of an 11 kg. dog and 125,000 in the kidney of another dog weighing about 8 kg. Peter calculated the number in the dog's kidney at 300,000. In the pig they are estimated at 500,000 by Schweigger-Seidl, and in the human kidney they are said to amount to 2,000,000 in number. The total length of the tubule is stated by Huber (1905) to vary from 1-3 cm., and the length of the various parts of three tubules isolated from the rabbit's kidney and measured by him (1911) were as follows :—

	Proximal Convoluted Tubule. mm.	From Capsule to the Thin Segment of Loop. mm.	Thin Segment of Loop. mm.	From Thick Segment to Collecting Tube. mm.	Total. mm.
A	6·8	11·3	1·4	7·8	20·5
B	5·6	9·4	6·7	6·9	23·0
	7·7	10·2	15·0	3·6	28·8

The most striking feature is the great variation in the length of the thin segment of the loop in any individual kidney, which is contrasted with the comparative uniformity in the length of the other parts of the tubule. It is stated (Peter) that in the dog and cat the loops are all long, and most of those in the rabbit also, while in man and the pig the loops are shorter and the thin segment of the loop is less developed.

The diameter of the lumen of the capsule and tubules varies greatly with the activity of the kidney. In hardened sections made from the resting organ there is generally little or no fluid apparent in the capsule; the epithelium covering the glomerulus lies almost in contact with that of the opposite side, so that the glomerulus practically occupies the whole space. The tubules also contain little fluid and the lumen is almost closed. On the other hand, in sections made from the kidney during diuresis, the glomerular capsule is separated from the opposite epithelium by a distinct layer of fluid, and the glomerulus itself is swollen by dilation of the vessels and also by fluid effused between these and the capsule covering them. The lumen of the tubules similarly increases to a marked extent. The following figures are drawn from an experiment of Brodie and Mackenzie (1914):—

	Resting Kidney. μ	Kidney during Diuresis. μ
Mean diameter of capsule	93·4	123·8
,, ,, glomerulus	90·4	100
,, ,, space in capsule	3·0	23·8
Lumen of proximal convoluted tubule	0·0	17·6
,, distal convoluted tubule	7·2	20 6

Many other changes have been described as occurring in the kidney during active secretion. Thus at one time the striated border of the epithelium was supposed to appear and disappear according to the degree of

activity of the cells. Large masses of granular matter were said to be extruded from the cells and to occupy the lumen (Metzner), but Rathery and Sauer regard these as artefacts caused in the course of fixation, and have in fact observed their development during this process. Undue weight has been laid upon the presence or absence of vacuoles in the cells as indicating their activity, and these have been described as emptying themselves into the lumen. But the most common statement is that the granules of the cells of the tubules are changed in character during diuresis, or even that they are developed during periods of rest and take the same active part in the secretion of the kidney as is seen in the salivary glands or pancreas. Others (Modrakowski, 1903) find the granules more irregularly arranged during diuresis, and Ophüls and others find them changed in size (see Suzuki, p. 192). Many of these supposed changes are unquestionably post-mortem in development, and careful observers have failed to observe any significant changes during activity. Thus Sauer (1895) in his investigations of the tubules found no changes of note in the appearance of the cells during diuresis. Similarly, Suzuki states that the only alteration is that the rods are more distinctly resolved into granules during diuresis. Aschoff points out that earlier writers have not recognized that the granules are unequally distributed in different segments of the tubules, and that this may explain some of the changes which have been held to occur during activity.

Hitherto no changes have been shown to occur during activity in the kidney except those arising directly from the distension of the capsule and tubules with fluid.

The lymph vessels of the kidney form a meshwork round the tubules and collect into larger trunks which issue from the hilus; lymph also escapes through a number of vessels which accompany the veins which issue from the convex surface of the kidney.

The anatomy of the kidney has been the basis of all the theories of renal secretion, and the characteristic feature, the glomerulus, has been almost universally credited with the function of secreting the water of the urine. The variety of epithelium lining the tubules has suggested that their function is a complex one, and some histologists appear to hold the view that absorption may take place in the thin part of the loop of Henle, while the character of the epithelium in the convoluted parts of the tubule suggests that secretion of some of the constituents may occur here. Due weight must doubtless be given to these arguments, but while the anatomical features may offer suggestions as to the function of an organ, it is impossible to accept these variations as offering definite evidence for or against any theory of renal activity. For example, the cells of the distal convoluted tubules resemble those of the proximal segment so closely that they have

very generally been confused. They might therefore be expected to have some resemblance in function, but Suzuki confines secretion to the proximal tubules and denies any such activity to the distal ones. Curiously enough, many of those that claim most loudly that similarity in structure indicates similarity in function, also support the view that such unlike structures as the capsule and the tubules secrete the same substances in the same way.

Nerves of the Kidney and their Function.

The nerve supply of the kidney is mainly derived from the semilunar ganglion, but small branches also run from the plexuses around the suprarenal body and the aorta, and as a general rule one twig comes from the splanchnic nerves direct. Through the semilunar ganglion the renal meshwork is brought into connection

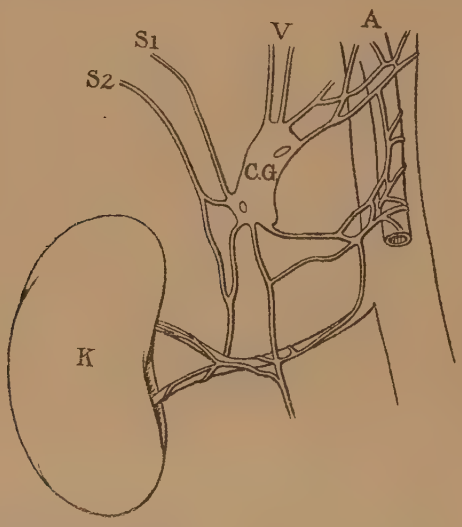

FIG. 4.—Nerve supply of the kidney (after Renner).
K, kidney. S_1, S_2, major and minor splanchnic nerves. V, vagus. C.G., cœliac ganglion. A, aorta.

with the splanchnic nerves and with the vagus, which also sometimes sends a direct branch to the kidney. These numerous branches form a plexus, known as the renal plexus, which is arranged in a network along the renal vessels, and in the kidney is distributed along the arterioles, small fibres occurring in the smallest afferent and efferent vessels and even on the capillaries.

Nerve fibrils have also been described on and between the cells of the tubules and capsule. Ganglion cells occur in large numbers on the renal plexus as far as the hilus, but Renner states that none occur in the kidney parenchyma. Sensory nerve terminations have also been described in the kidney. (A good description of the renal nerves is given by Renner, 1913.)

The kidney is thus innervated from the vagus and from the splanchnic, through the semilunar ganglion. The splanchnic fibres for the kidney leave the cord mainly from the sixth to thirteenth dorsal nerves, though some are found as far upwards as the fourth dorsal, and slight effects are obtained as low as the third and fourth lumbar nerves (Bradford, 1889). Other fibres are said to run to the kidney from the abdominal sympathetic (Jost), but this requires confirmation.

The splanchnic nerve has long been recognized to be the chief vasomotor nerve of the kidney. Bradford, who made a very detailed study of this subject by means of the oncometer, found that stimulation causes vaso-constriction in the kidney but that dilator fibres also occur in it, more especially in the eleventh to thirteenth dorsal fibres; these dilator fibres he recognized by means of very slow electrical stimulation, the kidney volume increasing, while the blood pressure remained unchanged or fell. On more rapid shocks the vaso-dilation was concealed by the stimulation of the vaso-constrictors of the kidney along with those of the other abdominal organs. Stimulation of the splanchnic trunk always causes vaso-constriction, the strongly represented constrictors masking altogether the feebler dilator fibres. Each splanchnic appears to be distributed only to the kidney of the same side (Burton-Opitz and Lucas).

The constriction of the renal vessels by splanchnic stimulation reduces or arrests the secretion of the urine. And until comparatively recently no serious question has been raised that this diminished activity is the result of the ischæmia alone.

Two papers by Rohde and Ellinger and by Jost have appeared which suggest that the splanchnic also acts directly on the secretory cells. The note by Rohde and Ellinger gives no details of their experiments, and their arguments appear to be based upon the characters of the urine secreted after section of the nerve; these differ in no respect from those of the urine under other forms of diuresis; and the view that the splanchnic contains fibres other than constrictors cannot be regarded as strengthened by their statement. Jost claims to have excluded the vaso-constrictor action of the splanchnic by

the injection of salt solution and theophylline, and still finds that splanchnic stimulation reduces the urine in the rabbit. In order to establish his thesis that the stimulation has an inhibitory action on the secretory cells, it would be necessary to demonstrate in each experiment that stimulation has no effect on the renal volume, and this he has not done. And the stimulation of the splanchnic naturally raises the blood pressure so that he could only judge of the inhibitory action by comparing the urine secreted by the kidney of the side on which the nerve was stimulated with that of the other ; the difference on the two sides is often absent in his experiments, and is certainly not great enough or constant enough to allow of any such inference as Jost draws.

Section of a splanchnic nerve was shown by Claude Bernard to be followed by an increased secretion of urine by the affected kidney, and this has been confirmed by practically all subsequent workers, and may be taken as established. Section of the splanchnics on both sides may reduce the blood pressure so far as to lessen the flow of urine, because though the renal vessels are relaxed, the blood accumulates in the other abdominal organs, and the supply to the kidneys is less than before the section.

The urine obtained after section of the splanchnic shows the same changes in character as occur in other forms of diuresis (see Chap. vii.).

The relation of the vagus to the kidney has been the subject of many investigations, but the results of careful experiments all point to one conclusion. Stimulation of this nerve in the neck causes a marked fall in blood pressure from the cardiac inhibition, and this is accompanied by diminution or total arrest of the secretion, as was pointed out by Goll and confirmed by Eckhard (1869). When the cardiac action is eliminated by stimulating the vagus fibres on the œsophagus, or by stimulating the nerves in the neck after atropine has paralysed the cardiac fibres, no change occurs in the kidney or in its secretion.

The absence of vasomotor changes in the kidney when the vagus is stimulated or divided without the cardiac fibres being involved, has been shown by Cohnheim and Roy, Bradford (1889), and Walravens by means of the oncometer. Burton-Opitz and Lucas (1911) confirmed this by experiments in which the blood-flow was measured by means of the stromuhr, and Pearce (272) has once more demonstrated it by the oncometer and by direct measurement of the outflow. Some observations by Masius and by Arthaud and Butte which they interpreted as indicating some action on the kidney directly or through its vessels, have been clearly shown to be based on errors in technique by the very careful work of Beco and Plumier and of Walravens. I would suggest to future investigators that a careful study of these last two papers would be a useful preliminary to embarking on this quest.

Quite recently Asher and Pearce have attempted to show that the vagus contains specific secretory fibres for the kidney, somewhat as the chorda tympani carries secretory fibres for the submaxillary gland. They stimulated the vagus fibres below the outflow of the cardiac branches for periods of about ten minutes, and compared the amount of urine secreted during these periods with that secreted in the intervals of rest. When the urine increased during the stimulation, it is claimed as evidence of the secretory effect of stimulation, when it increased in the intervals of rest it is claimed to be the result of a late action. The course of the secretion is further complicated by the continuous infusion of salt solution, and this may perhaps account for a rather irregular ebb and flow, which however by no means changes in the direction which would support their contention. A careful examination of their paper fails altogether to convince one that vagus stimulation has any effect on the secretion of the urine except that already mentioned as due to the cardiac inhibition.

Thus the voluminous literature on the influence of the renal nerves on secretion may be reduced to the short statement that the splanchnic nerves convey numerous vaso-constrictor and some vaso-dilator fibres to the kidney. Stimulation of the splanchnic trunk lessens the blood-flow through the kidney and therefore the secretion of the urine. Section of the splanchnic increases the blood-flow and the urine, which assumes the characters seen in other forms of diuresis. There are no grounds to believe that the splanchnic contains any renal fibres except these vaso-constrictors and vaso-dilators.

The vagus does not contain vasomotor fibres for the kidney. There is no evidence that it affects the secretion of the urine in any way except indirectly through its action on the heart.

The details of the action of the constrictor nerves on the vessels of the kidney are quite unknown; it is conceivable that it may be confined to the afferent or to the efferent vessels, or that it embraces both of these and the venules. If these different points are constricted separately by different fibres, the character of the urine must vary greatly through variations in the distribution of the blood inside the kidney, but as yet nothing is known of it; the only changes in the kidney which have been recognized, are the diminution in total volume, the fall in the venous pressure during constriction, and the change in the amount of urine.

Direct excitation of the vasomotor centre, as in asphyxia or in anæmia of the medulla oblongata, arrests the secretion of urine through ischæmia of the kidney. Reflex renal vaso-constriction is induced by stimulation of sensory nerves (Roy and Cohnheim,

Bradford), except the posterior roots of the lower dorsal nerves which cause vaso-dilation in the kidney. Bayliss points out that the vaso-dilators of the kidney are less developed than in the other internal organs, for when the depressor nerve is stimulated, the kidney volume falls parallel to the blood pressure, while the volume of the intestine and most other internal organs increases owing to the relaxation of their vessels. This observation may perhaps stand in some relation to one made by Gottlieb and Magnus, that under digitalis the constriction of the renal vessels is less marked than that of the mesenteric arterioles; digitalis is believed to act on the muscle of the walls rather than on the nervous structures.

Among the reflexes which diminish the secretion of the urine through constriction of the renal arteries, that arising from the application of cold to the skin is familiarly known and has been

FIG. 5.—Tracings of the blood pressure (B.P.) and renal volume (O) taken by oncometer, on the application of cold to the skin at the point indicated by the arrow (Wertheimer).

examined experimentally by Wertheimer and Delezenne; the former found the kidney shrink in volume, and the pressure and the blood-flow in the renal vein fall, owing to a reflex constriction of the arterioles when cold was applied to the skin (Fig. 5); this action on the kidney disappeared when the renal nerves were divided. Delezenne found the secretion fall in animal experiments when cold was applied to the skin, while the general blood pressure increased. This reflex vaso-constriction only lasts a short time, and is of course to be distinguished from the effects of more prolonged exposure to cold, which in man arrests the sweat secretion and thus leads to increased secretion of urine from the accumulation of water in the blood and tissues.

Another important reflex arises from the bladder and ureter, and not infrequently leads to complete anuria in man from the irritation induced by a renal calculus, or by the introduction of a catheter into the bladder or ureter. That the action is reflex is

often shown by the arrest of secretion in both kidneys from a disturbance affecting only one side. In this case the anuria can arise only from an arterial cramp in the kidney. Another change in secretion, which is also apparently reflex in nature, is the increase of the urine which is seen not infrequently in animals, and has been observed in man, when one ureter is slightly obstructed. The urine becomes more abundant than that of the unobstructed side and its composition is that common to all forms of diuresis—more abundant chloride, less marked acidity. This "pressure diuresis" disappears at once when the anæsthesia is deepened and is almost certainly due to a reflex vaso-dilation. It may be suggested that a slight stimulus arouses a dilator reflex, while a stronger one, such as the pain of a calculus, sets the more powerful constrictor apparatus in action and thus leads to anuria. Anuria from reflex excitation is a not infrequent clinical observation.[1] Diuresis from partial obstruction of the ureter has been described in man by Steyrer, Kapsammer, and others. In one case, Steyrer (1904) found that the introduction of a catheter into the ureter caused marked polyuria on the opposite side—a crossed reflex. Increased secretion is frequently observed in animals when the ureter is partially obstructed under light anæsthesia, or especially without anæsthesia in decerebrated animals (Brodie and Cullis, Pfaundler, Schwarz (1902), Lombroso (1910-11), Lucas (1908)); Brodie and Cullis attribute the diuresis to direct stimulation of the secretory cells by the increased pressure, but this will be discussed later. The explanation given above seems more probable, and until it has been shown to be erroneous, it is unnecessary to resort to special stimulation.

While the powerful effects of the renal nerves is to be taken into account in considering the activity of the kidney, it must be added that the secretion continues for many months, perhaps indefinitely, after all the connections with the central nervous system have been divided. Further, Carrel and Guthrie have transplanted the kidneys of a dog into a bitch and removed the kidneys of the latter, without fatal results; here the kidney carried on its functions for many days without any possible guidance from the central nervous system. Others have transplanted the kidney into the neck or grafted it on to the splenic vessels, where

[1] Some literature on the subject is briefly given by Goetzl, who also attempted to induce crossed reflex anuria in dogs, without much success.

it retained its activity though all nervous connections were divided (literature given by Lobenhoffer).

The latest work in this direction is that of Quinby (1916), who excised one kidney in the dog and then replaced it, suturing the vessels and ureter. On comparing the secretion of the two kidneys a few days later, the operated one was found to secrete more than the other; this is in accord with the observations of others that division of the renal nerves increases the secretion; later the urine became equal on the two sides. The efficiency of the denervated kidney was shown by the animals surviving indefinitely after the other normal kidney had been excised, without any increase in the urea of the blood or any delay in the excretion of test substances.

While stimulation of the medulla oblongata by asphyxia diminishes the urine by vaso-constriction, Claude Bernard showed that puncture of the floor of the fourth ventricle a little above the "glycosuria point" causes polyuria, and this has been confirmed by later workers (Eckhard, Kahler, Finkelnburg). The polyuria is of comparatively short duration and is believed to arise from stimulation of some centre rather than from its destruction; but this is not by any means established. Polyuria is met with clinically from various forms of lesion of the brain, especially from fractures of the skull and tumours, and attempts are made to relate these to the puncture polyuria, while some writers are inclined to ascribe most of these central polyurias to stimulation direct or indirect of the pituitary gland (see Diabetes insipidus).

Bechterew states that the secretion of urine may be altered from the cerebral cortex, and this is in accordance with the frequent clinical observation of diuresis after epilepsy, headache, or hysterical excitement.

CHAPTER II.

THE CHIEF CONSTITUENTS OF THE URINE AND THEIR CONCENTRATION.

Concentration in the urine and blood of normal constituents—of foreign substances—"threshold" and "no-threshold" bodies—water—Ambard's volume obligatoire—physical factors in secretion.

THE kidney does not form any specific constituent of its secretion (except hippuric acid) as the liver does, but merely eliminates unchanged such bodies as are brought to it by the blood. But while the constituents are unchanged in form, the relative proportions in which they appear in the urine are greatly altered, as is shown in the following table, in which the percentage composition of the blood plasma is compared with that of an average sample of human urine.[1] In the third column the change in the concentration is shown for each constituent that is excreted in the urine.

	Blood Plasma, per Cent.	Urine, per Cent.	Change in Concentration in Kidney.
Water	90—93	95	—
Proteins, fats, and other colloids	7—9	—	—
Dextrose	0·1	—	—
Urea	0·03	2	60
Uric acid	0·002	0·05	25
Na	0·32	0·35	1
K	0·02	0·15	7
NH_4	0·001	0·04	40
Ca	0·008	0·015	2
Mg	0·0025	0·006	2
Cl	0·37	0·6	2
PO_4	0·009	0·27	30
SO_4	0·003	0·18	60

[1] Similar proportions hold in general throughout the mammals, the chief differences being in the uric acid, for which allantoin is largely substituted. The analysis of frog's urine is given by Toda and Taguchi, while Denis gives that of the urine of several fish.

The relative proportions in which the several constituents appear in the urine is very different under normal conditions and may show still greater contrasts when any of them occurs in large quantities in the blood.

The proportion of water and total solids is often very similar in plasma and urine, but when water is taken in large quantities the urine shows greater changes than the blood and the solids may sink to 1 per cent or less. On the other hand, when little water is taken, or when it is eliminated in large quantities by the skin or bowel, the blood remains practically unchanged, while the urine may become very concentrated.

There is almost always sufficient water eliminated to keep the solids in solution, the chief exception in normal life being the turbid urine of the herbivora, arising from the presence of insoluble salts of the alkaline earths.

But while the percentage of solids in blood and urine may be nearly equal, the great mass of solids in the blood consists of proteins and colloids, while the solids of the urine are formed of salts and small organic molecules. The molecular concentration, that is, the total number of molecules in a given quantity of fluid, is much higher in the urine than in the blood under ordinary conditions. This molecular concentration may be determined by the depression of the freezing-point of a fluid below that of distilled water. The depression (Δ) for blood is almost constant at $-0.56°$ C., while the urine ordinarily possesses a Δ of $-1°$ to $-2.5°$. Concentrated urine may, however, freeze only at a temperature of $-5°$, while, on the other hand, in the dilute urine after profuse water drinking the depression may be only $-0.075°$.

Proteins, fats, and other colloids which comprise the chief solids of the plasma, do not escape through the normal kidney.

Dextrose is also retained in the blood except a trace, which is found in the normal urine, and which may be regarded as evidence of imperfection in the kidney rather than as a purposive secretion. When the content of sugar in the plasma rises to 0.2-0.3 per cent, however, it begins to pass into the urine, and its percentage may rise to 10 per cent or more, the kidney thus concentrating it about 50 times.

Urea is always present in urine, and always in higher concentration than in the plasma as far as is known. In human urine it hardly rises above 4-5 per cent, but in the carnivora it may

reach 10-15 per cent, the kidney raising its concentration about 150 times.

Uric acid also occurs in the urine in man in higher ratio than in the plasma under normal conditions, but the extent to which the kidney concentrates it varies greatly. In the other mammals, uric acid forms a smaller constituent of the blood and urine, while in the birds it occurs up to 0·01 per cent in the plasma and is present in high concentration in the urine of the ureter. Any increase in the flow of urine in the bird is accompanied by an increase in the total amount of uric acid excreted, but the water rises in greater proportion so that the percentage of urate falls (Robertson).

Creatinin and amino-acids appear in the urine, but exact analysis are not available ; the percentage of creatinin is certainly higher in the urine than in the plasma,[1] and according to some recent analyses the kidney concentrates it more efficiently than urea even.

Among the inorganic constituents sodium occupies a special position. It is not infrequently present in approximately the same percentage as in the plasma, but when the food contains large quantities, it may rise to about 2 per cent. On the other hand, it may disappear completely when little salt is taken, and also in certain acute inflammations, such as pneumonia ; it is still unsettled whether this arises from the lack of food containing sodium (Sollmann, 1902), or from more obscure conditions. The percentage of sodium in the blood plasma remains practically unchanged whatever the amount in the urine may be ; any marked deviation is, in fact, incompatible with life.

Potassium is concentrated in its passage through the kidney to a varying extent, but is generally present in the urine in higher percentage than in the plasma. Comparatively few estimations of the potassium of the urine have been made, but from those available, it appears that the kidney concentrates potassium much more regularly than sodium.

Ammonium appears in the urine in much higher concentration

[1] The proportion of urea to the total non-protein nitrogenous bodies is much higher in the urine than in the blood. Thus the nitrogen of urea makes up about 40 per cent of the total non-protein nitrogen of the blood, that of the mono-amino-acids rather less than 40 per cent, while in the urine the urea nitrogen is 80 per cent of the total nitrogen and that of the amino-acids only 3 per cent.

than in the plasma according to the estimations of its amount in the latter; in fact, the extent of concentration is exceeded only by that of urea and the sulphates, and further examination of the content of ammonia in the plasma may place it on the same level as these.

Calcium and magnesium appear from the table to be only slightly concentrated by the kidney, but this may probably arise from the percentage given for the plasma being that of the totals present and not that of the free ions. For much of the calcium, and probably of the magnesium, of the plasma is associated with the proteins and other colloids, or may be itself in a colloid form, and thus escapes the activity of the kidney.

The chloride ion resembles the sodium in its great variability in the urine. It may be present in about the same concentration as in the plasma, or slightly higher, or it may rise to about 2-3 per cent, or sink to zero (Grünwald) in the same way as the sodium ion, and often in the same conditions. It is important to note, however, that the chloride content of the urine cannot be taken as indicating the amount of sodium present. For a variable proportion of chloride is combined with potassium, and as the excretion of potassium differs greatly from that of sodium, it is erroneous to express the results of chloride determinations in terms of NaCl as is frequently done.

The phosphates and sulphates are concentrated in the urine in about the same proportion as the urea, as far as can be stated from the insufficient analysis of the plasma, for these deal only with the totals present and not with the free ionic radicles.

A further change occurs in the kidney in the reaction to indicators, but this will be discussed in a later chapter (see Chap. x.).

The urea, ammonium, phosphate, and sulphate thus appear in the urine in much higher concentration than in the plasma; uric acid and potassium are not concentrated to the same extent; sodium and chloride show a comparatively small change in percentage, while dextrose and the colloids fail to pass the kidney.

In addition to the ordinary constituents of the blood, the kidney eliminates a vast number of other substances which enter the circulation incidentally. Thus almost all the salts of the alkalies and alkaloids and innumerable neutral bodies are found in the urine when they have reached the blood stream. In fact, it is easier to enumerate the exceptions to the rule than those

that conform to it; among these exceptions may be mentioned morphine and some of the heavy metals such as iron, bismuth, copper, and zinc, which are excreted by the intestinal epithelium almost exclusively, some neutral lipoid-soluble substances which appear by preference in the bile, and very volatile substances with a low solubility in water which are often eliminated by the lungs (ether, chloroform).

As a contrast to the wide powers of selection of the kidney, the strictly limited field of the gastric glands may be mentioned, but there is, in fact, no tissue of the body which possesses the same catholicity as the kidney, except the intestinal epithelium, which is capable of absorbing at least as diverse substances.

One criterion which determines the suitability of the kidney as an organ of elimination is the solubility of a substance in water. But this is not the only necessary feature, otherwise morphine would be excreted by the kidney as well as strychnine and codeine (methyl-morphine), and iron would appear in the urine as readily as mercury and lead. The characters which exempt these exceptional substances from passage through the kidney have not been surmised at present. Substances of a colloidal character seem to pass out by the kidney with greater difficulty than those in true solution.

The enormous number of substances which pass through the kidney seems to preclude the possibility that its selection is governed by any chemical combining powers, and suggests that here the physical processes are the determining factors.

The elimination of most of these foreign bodies by the kidney appears to follow the same course as that of the waste products, such as urea, and though no accurate comparison of their concentration in the urine with that in the plasma has been made, there is no question that they are highly concentrated in their passage through the kidney.

As regards their concentration in the kidney, then, the constituents of the urine form a series of which one extremity comprises urea, foreign bodies, sulphates, phosphates, and ammonium, while the other is represented by chloride, sodium, and dextrose: intermediate positions are occupied by potassium and urate, while calcium and magnesium are not sufficiently known. The class of which urea may be taken as a type is present in much higher concentration in the urine than in the plasma, and its elimina-

tion appears to depend directly on the absolute amount in the plasma; that is, urea is excreted as long as any is present in the blood. This cannot be proved directly for urea, which is constantly being replaced from the tissues, but has been shown for other substances which resemble it in their mode of excretion. Thus Michaelis and Mass have shown that the amount of boric acid in the urine depends on the concentration in the plasma, and have given this simple law the dignity of a mathematical formula. The graph in Fig. 6 is drawn from the figures given by Anten for the excretion of iodide, the amounts available in the tissues being calculated after Michaelis, by subtracting that

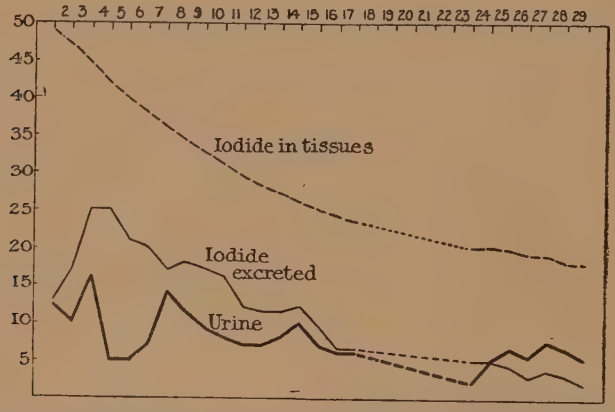

FIG. 6.—Graph of iodide excretion in the urine (after an experiment of Anten). Time in hours, iodide in milligrams. The amount in the tissues is calculated by deducting the amount already excreted from the dose given.

already excreted from the total ingested. It will be seen that the two curves run fairly parallel after the absorption of the drug was complete. The amount in the plasma therefore determines the amount in the urine for this class of body.

Dextrose, chloride, and sodium at the other extremity of the series behave differently, for in these the amount in the urine ordinarily bears no direct relation to the absolute concentration in the plasma. When the amount of these bodies in the plasma falls below a certain threshold (Ambard) they cease to pass into the urine. The dextrose of the plasma is normally below this threshold, and it is therefore not present in normal urine; the sodium and chloride also possess a threshold, but this is more frequently exceeded in normal conditions and the excess is then

eliminated. Thus when the sugar of the plasma runs to 0·3 per cent it appears in the urine, and seems to undergo concentration in the kidney in the same way as urea; and similarly when chloride exceeds the threshold value it escapes in the urine. In comparing the degree to which the kidney concentrates the several constituents of the plasma, this threshold value must be taken into account. Urea has no threshold and the concentration is thus determined by comparing the percentage in the plasma and urine directly. But chloride possessing a threshold below which it cannot fall in the plasma, the change in concentration caused in the kidney can be obtained only by comparing the excess over the threshold in the plasma with the concentration in the urine. When this is done, the concentration of chloride in the kidney is probably of the same order of magnitude as that of the urea in any given sample of urine. The rule would then run—

$$\frac{C_B - T}{C_U} = k,$$

where C_B and C_U represent the percentage of any constituent in the blood and urine respectively, T is its threshold value in the plasma, and k is a constant for each sample of urine. This formula holds also for urea and similar solids which have no threshold value, but here T disappears, and k is the ratio between the total concentration in the blood and that in the urine.

The relation between the chloride of the plasma and of the urine cannot be followed very exactly, but bromides resemble chlorides closely, and in Fig. 7 the graph of bromide excretion is represented in the same way as that used for the iodide in Fig. 6. The amount excreted is not so nearly parallel to the total in the tissues as appears in the case of the iodide.

Potassium and uric acid form an intermediate group in regard to their concentration in the urine as compared with that in the blood, the ratio being lower than that of urea and higher than that of chloride under ordinary conditions. This merely indicates that they have a threshold in the plasma below which they are not excreted, but which is more constantly exceeded than that of sugar and chloride. It is known that potassium is an essential constituent of the plasma, and there is therefore every reason to maintain it above a certain level. As long as uric acid was regarded merely as a waste product and poison, it would have

seemed strange to assign it a threshold in the plasma like sugar; but it is now considered rather an intermediate phase rather than the final product of metabolism, and only the excess escapes in the urine.[1] According to Burian and Schur (1901), about half of the uric acid that reaches the blood in man is eliminated in the urine, in the rabbit only one-sixth, and in the carnivora only about one-twentieth; the rest undergoes further metabolic changes.

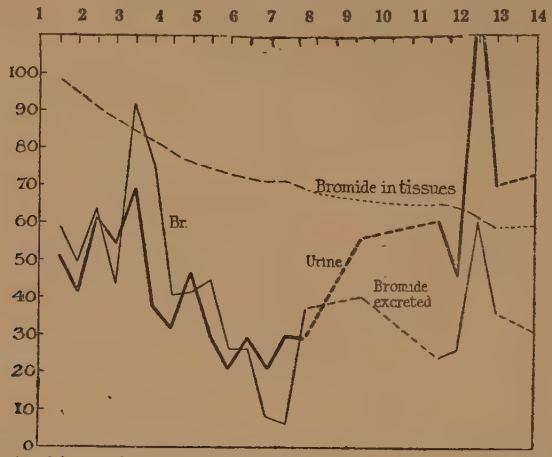

FIG. 7.—Graph of bromide excretion in the urine (after an experiment of Hale and Fishman). The amount in the tissues is estimated in the same way as for the iodides in Fig. 6. Time in days.

The fact that some constituents of the plasma are only excreted in as far as they exceed a certain threshold value, while others are excreted in proportion to their absolute amount in the plasma, has an important bearing on the views regarding secretion and will be met again later. I shall distinguish the first group as the *threshold bodies* from the second or *no-threshold bodies.*

It is often stated that the kidney eliminates the waste products such as urea while retaining those constituents of the plasma whose loss would entail a departure from its normal composition. This is merely a teleological expression of the facts given in the last few paragraphs, but as it suggests a certain intelligence on the part of the kidney, it is perhaps better avoided.

Urea and uric acid are often termed the specific constituents of the urine, apparently because they occur in larger amounts in it than elsewhere, but they are by no means characteristic of the urine in the sense in which bile

[1] It is still undecided whether the urate of the blood is all in true solution or whether its colloid form may not account for its failure to be excreted *in toto* in the urine.

salts are characteristic of the liver secretion. They are eliminated by the kidney in the same way as many other bodies, such as the phosphate and sulphate, and may be exceeded in quantity in the urine by dextrose, which is certainly not a specific urinary constituent. The special position assigned to urea appears to date from the time at which urea could not be formed synthetically and was believed to arise only in living matter. Now that urea is formed artificially, it has been robbed of much of its mystery, and there is no reason to suppose that it differs fundamentally from the salts in its behaviour in the kidney. It is quite possible that the various constituents of the urine may follow different paths through the kidney, but in all probability this is determined not by their chemical structure directly, but by their physical properties, such as their tendency to diffuse into living cells.

The elimination of one constituent of the plasma which is present in excess does not necessarily involve changes in the others. For example, salt added to the food is excreted in the urine and the total chloride increases, but the amount of urine and of the other constituents may remain unchanged; the percentage of chloride of course increases. But it not infrequently happens that excess of salt in the food leads to an increase in the water of the urine, and the percentage of salt in it remains unchanged while the total salt rises; the other constituents remain with little change in absolute amount, but their percentage falls from the increase in the water. This variation in the behaviour of the kidney to salt is probably more apparent than real. For the salt is presented to the kidney not as it was ingested but as it occurs in the plasma; if the salt has passed into the blood without much disturbance of the circulation of the blood and lymph, it comes to the kidney in the form of a slight excess of chloride in the plasma. But if exchange currents have been set up between the tissues and the blood, the plasma reaching the kidney may have excess of both water and salt, and both are eliminated together. The difference in the reaction arises from the varied activity in the tissues in general and not from inconstancy in the kidney.

Water is often treated as separate from the other constituents of the urine, but really resembles them in most features, though it is more frequently present in excess in the ingesta and is eliminated in larger quantities by other organs, and therefore is subject to greater variations in the urine than the other constituents. Further, water, circulating in the blood and lymph, washes out the waste products, so that the plasma becomes enriched

with these, and the kidney responds by eliminating them in larger quantities than usual. The water increase is often very great, while the other constituents rise slightly in total but fall greatly in percentage.

But in addition, the water of the urine bears a special relation to the other constituents which does not exist among the solids. The kidney must always excrete these in solution, and further it can only concentrate them to a limited extent. Thus the alkali chloride of the urine rarely exceeds 4 per cent in the rabbit or in man, and the urea as a general rule hardly rises much higher. In dogs fed on meat and supplied with water, Ambard and Papin find a surprisingly uniform percentage of urea even when the total per day varies. The same is true in the cat, the percentage of urea remaining constant for weeks if the animal receives the same amount of meat and is allowed as much water as it desires; the actual percentage varies with the individual animal; Ambard found in the dog 1·8 to 10 per cent, while in individual cats I find it from 9 to 15 per cent, but some cats may have a more limited power of concentration than those I have examined. If urea is supplied by the mouth, the total in the urine rises but the percentage remains unchanged. On giving water by the mouth in large quantities the percentage of urea falls, while salt given in the same way has little effect on either water or urea in my experiments, though the percentage of chloride rises.

There is thus a limit set to the power of the kidney to separate the water from the solids of the plasma, for the solids of the urine require the presence of a definite amount of water which has been termed by Ambard the "volume obligatoire". The limits of concentration have only been examined for urea as yet, and that not completely. It is probable that other substances in the urine may also exercise the same influence on the water excretion. For example, the sugar in diabetes sometimes reaches as high as 10, and, it is said, even 15 per cent, and this may also be the limit to which the kidney can concentrate it. These limits of concentration appear to be fixed by the energy which the kidney can bring to act against the osmotic resistance. How great this energy is, is shown by the fact that 10 per cent urea opposes a resistance of about 28 metres of mercury (over 35 atmospheres) to further concentration; yet the cat's kidney easily overcomes this.

Physical Factors in Secretion.

No one now attempts to explain the secretion of the urine by the known physical forces, yet in any consideration of the function of the kidney these forces must be taken into account, partly as acting in the same direction as the vital activity of the cell, partly as offering a resistance which it has to overcome. A short account of the physical processes occurring in solutions may therefore be given as far as they concern the passage of substances through cells; these are the same whether the direction of the current is from the blood (secretion) or towards the blood (absorption). In either of these the process consists of three phases, the first consisting of the passage of the body into the cell, the second of its transmission through it, and the third of its extrusion on the other side.

In the first of these, the physical conditions play the dominating part; for, quite apart from the various views regarding the secretion of the kidney, it is beyond doubt that the renal cell is quite passive in its reception of substances from the surrounding fluid. The mere fact that it is bounded by a basement membrane precludes it from any activity such as is displayed by the naked leucocytes. The permeation of the renal cell by water or salts is thus of the same nature as the permeation of moist discs of gelatin, and obeys the laws of diffusion equally. If such a disc is placed in a solution of indifferent salts which are able to penetrate into it, they diffuse into it rapidly, and the disc soon contains exactly the same concentration as the fluid in which it is immersed; the whole becomes homogeneous as far as the salt and water are concerned; the gelatin can never contain a higher percentage of salts than the fluid unless other processes than diffusion occur.

If, however, the solution contains one or more salts which cannot permeate the gelatin, a different result follows. As these salts cannot penetrate into the gelatin, the water in which they are dissolved is also held back; for if the water entered the disc while the salts remained in the solution, the latter would become more concentrated. Now in order to concentrate a solution energy must be used, and under these conditions there is no source of energy available. This osmotic resistance to the passage of water when it contains impermeable substances in solution may

be overcome by external pressure exerted on the fluid. Or, if the gelatin contains salts in concentration greater than that of the surrounding fluid, these may exercise sufficient pressure to draw water into the disc even against the resistance of the non-permeating salts. There is then a struggle for the possession of the water between the salts in the interior of the disc which cannot escape from it, and those on the exterior which cannot enter it, and the heavier battalions carry the day, the water passing in the direction of the greater concentration. In the meantime the salts of the solution which are able to permeate gelatin pass into it as if they were unaccompanied by non-permeating substances.

The concentration of such a substance as urea in a disc of gelatin, or in the renal cell, is thus limited by that of the surrounding fluid, if it enters the cell by diffusion and continues in solution in the cell contents. On the other hand, if it is thrown out of solution by forming some chemical compound or by adsorption on intracellular surfaces, the quantity in the cell may rise indefinitely, though the concentration in solution in the cell fluid remains the same as that of the fluid from which it is derived. This accumulation in the interior of a renal cell through deposition in insoluble form does not occur in the case of urea in all probability, but certain dyes are certainly assembled in considerable amount in this way, as will be shown later.

The second phase—the transmission through the cell body—may also occur by diffusion, and the same limitations apply here, the cell can only contain the same concentration as the original fluid. If all the constituents can permeate the cell, they may in fact pass completely through it by diffusion and appear on the other side in the same concentration as they entered. Or if some of them cannot permeate the cell, and thus exercise an osmotic resistance to the entrance and transmission of the solvent, this may be overcome by the application of pressure sufficient to overcome this resistance, and the cell thus acts as a filter allowing the water and permeating solids to pass through while refusing passage to those by which it is impermeable. In all of this, however, there can be no concentration of the constituents that pass through the cell. They are present in the same percentage in the diffusate, or in the filtrate, as in the original solution.

The concentration of a solution in its passage through a membrane demands the consumption of far more energy than is sup-

plied by the known forces in the kidney, and the concentration of the urine has therefore to be attributed to the vital activity of the cells. The nature and method of action of this vital force is unknown, but it may be conceived as wafting the molecules which diffuse into the cell, through its network somewhat in the way in which the cilia carry forward particles of dust that fall on them. This onward movement of the molecule leaves the point at which it entered the cell free for the diffusion of another molecule, which follows its precursor and is transmitted through the cell in the same way. This transmitting force can of course act only upon those constituents which have diffused into the cell; a single constituent of the fluid may enter and be carried through the cell, or the whole of the fluid may be subjected to the vital activity.

The transmission through the cell may possibly demand very little expenditure of energy—that is quite unknown. But the extrusion on the surface, the third phase of the process, is subject to osmotic conditions which may be calculated, and which may offer a very high resistance to the extruding vital force. For example, a molecule of urea may be supposed to diffuse into a tubule cell and to be caught in the transmitting machinery and hurried to the lumen of the tubule. The inner surface is permeable by urea, otherwise the molecule could not be extruded. But the lumen contains urine with 10 per cent of urea (in the cat), and its molecules are battling for entrance to the cell with a pressure of over 35 atmospheres.[1] The force which extrudes the molecule thus works against a pressure of 35 atmospheres. According to another view, molecules of water are taken up from the tubules and carried to the plasma. Here the cell surface towards the lumen is conceived as permeable by water but not by urea, and the water in the cell is drawn towards the interior of the tubule with a pressure of 35 atmospheres, which must be overcome by the transmitting force before any water can enter the cell on its way to the blood. Whichever view be accepted, it is obvious that the change in the concentration entails a very large expenditure of energy on the part of the cells. And

[1] A molar solution, that is, one containing in a litre as many grammes as the molecular weight of a substance, exerts an osmotic pressure of 22·4 atmospheres. Thus a 1 per cent solution of urea has an osmotic pressure of ($\frac{1}{60}$ × 22·4 =) 3·7 atmospheres, or about 2·8 metres of mercury; 0·025 per cent of urea in the blood plasma exercises an osmotic pressure of about 70 mm. of mercury and 0·1 per cent of dextrose about 95 mm.

this takes account only of that employed at the boundaries of the cells in overcoming osmotic resistance and neglects that which may be necessary for the transmission through the cell.

It is conceivable that each constituent of the urine is excreted by a different set of cells in the kidney. But this would be a very wasteful procedure; for if one cell is supposed to excrete sodium chloride alone, it devotes a large amount of its energy to the separation of this salt from the water in which it is dissolved, while a neighbour entrusted with the elimination of water must devote the same amount of energy to separating the water from the chloride. The greatest economy of energy is effected if the largest possible number of constituents escape together through the same cells, so that no energy is wasted in effecting a separation, which is afterwards to be undone by reunion.

In this conception of the passage of a molecule through a cell, the vital activity plays a simple part, merely setting in motion a current through the cell which produces a sort of vacuum at the absorbing pole, while it drives out the molecules at the other. It may of course be a much more complicated process, but it is unnecessary to suggest further machinery unless this simpler one proves insufficient.

The movement has been considered only of bodies in solution in the cell fluids, and therefore in separate molecules, and the concentration of the transmitted substance can never exceed that in the lymph from which it is drawn. The concentration is effected in the fluid outside the cell by the extrusion of additional molecules, one after the other. It is quite possible, however, that a substance may enter the cell by diffusion and be deposited in solid form in its interior and thus no longer exercise any osmotic resistance to the arrival of further quantities; this, in fact, occurs in the formation of various concretions (e.g. of lime) in the interior of cells. When such a deposit occurs in a cell, further diffusion of the same substance may go on and the secretion of the diffused molecules may continue as before; the concentration of the secreted substance in solution in the cell cannot exceed that in the lymph, but the total amount in the cell may be much higher. If the diffusion ceases for any reason, for example, if the supply in the lymph runs short, the secretion may continue, because the deposit in the cell is now drawn into solution gradually. If a substance is only supplied intermittently and is deposited in the

cells, the delivery may thus be rendered more regular than if it is not so deposited. Otherwise the process of alternate deposition and re-solution appears to present no appreciable advantages to the cell. Some authorities, however, seem to consider that this "concentration" of the urinary substances within the cells is necessary to explain the fact that they occur in larger quantities in the urine than in the lymph. But as has been pointed out above, secretion by separate molecules is sufficient to explain such a change of concentration between lymph and urine, provided the necessary energy is available.

Various forms of deposit in the renal cells have been described ; granules of uric acid have been recognized in the cells of the contorted tubules (Sauer, 1899), while Gurwitsch (1902) and Höber and Königsberg (1905) have described dyes as deposited or adsorbed on the cell granules or as dissolved in the interior of vacuoles. Most of these authors hold that these aggregates then move through the cell until they reach its frontier, when the contents are emptied into the lumen ; it is of course quite possible that these masses may be moved forward by the same intracellular mechanism as has been assumed for the movement of dissolved molecules, but there is not a scintilla of evidence that either granules or vacuoles move in the renal cell. It is tacitly assumed that the deposition of the dyes is a step in the process of secretion, and the validity of this assumption will be discussed later. But even if it be granted for the moment that the dyes are deposited on their way from the blood to the urine, the movement of the granules or vacuoles does not necessarily follow, for the dyes may merely be deposited temporarily in them to be redissolved in the cell fluids, as the excess is got rid of by the secreting currents. It is conceivable indeed that there may be a series of such stations in a cell through which the dye passes, each one yielding its content as the cell fluid in front of it empties itself of its dissolved dye. The difficulty in the conception that the deposits move bodily through the cell and are ejected at the frontier lies in disposing of the substrate in which the dye is embedded. For there is no evidence of any such substratum in the urine into which Gurwitsch and Höber suppose the granules and vacuoles to enter, and these authors have to resort to further unsupported assumptions to explain its absence. No such difficulty is met with if the deposits are regarded merely as temporary concentrations, from which and to which the dyes are transported in solution. And some evidence in favour of this is offered by an observation made by Höber and Königsberg ; some of these dyes are precipitated by ammonium molybdate, and these authors observed that if a dead cell containing vacuoles coloured with these dyes is immersed in a solution of this salt, the coloration of the vacuoles disappears and the cell becomes surrounded by a layer of precipitated dye. Here there can be no question of the movement of the vacuole, for the cell is dead ; the molybdate cannot permeate the cell, but the dye diffuses through the cell from the vacuole, and reaching the molybdate is precipitated ; this removal of the dye from solution allows further

diffusion and the dye thus finally disappears from the interior of the cell. I suggest that the precipitation of the dye here has the same result as is effected during life by the cell currents.

These conceptions of the movements of the contents of cells are equally applicable whether these are concerned with secretion or absorption. In fact, Höber and Königsberg obtained the same results from intestinal cells, which are certainly engaged in absorption and from cells of the contorted tubules, which they regard as excretory; they conclude that in each the permeability is the same.

CHAPTER III.

THE WORK, GASEOUS METABOLISM AND BLOOD SUPPLY OF THE KIDNEY.

THE urine is generally more concentrated than the blood serum if freed from proteins, and a certain amount of work is accomplished by the kidney in forming this concentrated solution. The energy used by the kidney in the actual work of concentration may be calculated according to known physical principles, and is the same as would be necessary in changing the concentration by other means. The first to make such an estimation was Dreser, who in 1892 applied to this problem the theory of solutions then recently stated by Van't Hoff. He determined the molecular concentration of the blood serum and of the urine by the depression of the freezing-point (Δ) of each compared with that of distilled water. Serum was found to possess an almost constant Δ of $-$ 0·56°.[1] Urine varied greatly, but one sample which he discussed had a Δ of $-$ 2·3°. The problem, as he conceived it, was to determine the work necessary to change a fluid of Δ $-$ 0·56° to one of $-$ 2·3° by the withdrawal of water. He used for this purpose the formula[2]

$$A = 100\, a\, (\log x_1 - \log x_2)$$

where A is the work, a the solids in the original, and also in the final solution, x_1 the amount of original fluid, and x_2 that finally remaining. According to this formula, the work done against osmotic resistance in forming 200 c.c. of urine of $\Delta = -$ 2·3° from blood serum, amounts to about 37 kilogram-metres. When the urine is less concentrated than the blood serum, work is also done against osmotic pressure, in this case the solids being retained and the fluid secreted. In one example

[1] Corresponding to a pressure of about 5 metres of mercury or 7 atmospheres.

[2] The logarithms in this and the following formulæ are natural logarithms to the base e.

in which the urine had a Δ of only $-0{\cdot}16°$, Dreser estimated the work at 49 gram-metres for each gram of urine.

This method of Dreser's was later developed by Galeotti, who employed a more complicated and more accurate mathematical formula,

$$A = \frac{RT}{1850} V \left(\Delta_1 \log \frac{\Delta_1}{\Delta_0} - \Delta_1 + \Delta_0\right)$$

in which A is the work done, R the gas constant, T absolute temperature, V the volume of the urine, Δ_0 the depression of the freezing-point of the blood serum, and Δ_1 that of the urine.

This formula applied to the example given by Dreser gives the work of the kidney as 42·91 kgm. instead of his estimate of 37 kgm.

These ingenious observations have, however, little relation to the work actually performed by the kidney. For the work measured by Dreser and Galeotti is only that necessary to evaporate the protein-free blood serum to about one-fourth of its original volume. The fluid remaining would have the same concentration as the urine, but would otherwise differ from it entirely. For in the kidney not only is there a process of concentration, but the different constituents are concentrated in different ratios; and these mathematical formulæ take no account of this whatever. In Dreser's example, the work which he calculated would have resulted in the formation of a fluid containing about 3 per cent of NaCl and 0·4 per cent of urea, and the other constituents in proportions equally far from those ordinarily found in the urine. Theoretically this method of measuring the work of the kidney in the secretion of urine is inadmissible, for it does not give the work of concentration taken alone even approximately. And Barcroft and Brodie (1905) found it bear as little relation to the oxidation in the kidney, the work calculated by Galeotti's formula never amounting to more than a small fraction of the chemical energy employed as measured by the gas exchange.

In order to measure the work done by the kidney in concentration it is not sufficient to compare the total molecular concentration of the blood serum with that of the urine; the change in the concentration of each individual constituent must

be determined, and the sum will then represent the actual work done in the process of concentration. This is at present impossible, as the exact concentration in the blood and even in the urine is known for comparatively few substances. Rhorer (295) has calculated the work necessary for the concentration of the sodium chloride and urea by the kidney in an example; if the blood contains 0·6 per cent NaCl and 0·06 per cent urea, and the urine 1·2 per cent NaCl and 2·4 per cent urea, the work done in concentrating the chloride in a litre of urine would amount to 18·28 mkg., that in concentrating the urea to 290 mkg.; or the whole to 308·28 mkg. The Dreser-Galeotti formula would give only 127·2 mkg., or little more than one-third of that for chloride and urea only.

But even this larger figure gives a very inadequate idea of the work actually performed by the kidney, and it seems not an over-estimate that the secretion of 1000 c.c. of ordinary urine may entail at a minimum work of 500 mkg. exerted in the process of concentration. A formula for the actual calculation of the work of concentration if all the constituents of the urine are estimated, is given by Magnus (1909) from Bredig's calculations, and a similar one has been elaborated by Hill at Barcroft's instigation (1914).

According to the latter, if the blood contains various constituents in the molecular concentrations a_b, b_b, c_b . . . and the concentrations in the urine of these are a_u, b_u, c_u . . . , the minimum work (A) in forming a litre of urine may be calculated as—

$$A = RT\left[a_u \log \frac{a_u}{a_b} - (a_u - a_b) + b_u \log \frac{b_u}{b_b} - (b_u - b_b) + \ . \ . \ .\right].$$

In shorter terms, if c_u be taken as the concentration in the urine and c_b that in the blood of any constituent, this formula may be summarised as—

$$A = RT\left[\Sigma\left(c_u \log \frac{c_u}{c_b}\right) + \Sigma c_b - \Sigma c_u\right].^1$$

But even if the concentration of each constituent of the plasma and urine was known, and the total work was calculated according to these formulæ, this would not necessarily indicate the whole energy employed in the secretion. For this measures

[1] I am indebted to Prof. Donnan for this formula as well as for other help in this chapter.

only the energy employed in overcoming osmotic resistance, and takes no account of that entailed by the actual transmission of molecules of water and solid through the cells and along the tubules. Nor until more is known of the mechanism of secretion, can even a general estimate be formed of the amount of energy thus used. For example, two samples of urine differing in amount may contain the same quantity of solids and in the same relative proportions; they differ only in the amount of water. Now if, as one school holds, the secretion of water involves actual work on the part of the cell, more energy is required for the production of the more abundant fluid, but as it is less concentrated the work done against osmotic resistance is smaller. The total work of the kidney in producing a dilute urine may thus be greater or less than when it is more concentrated, according as the energy required to secrete water is greater or less than that required to concentrate the solids. On the other hand, if the secretion of water does not entail the loss of energy in the kidney, as is held by some authorities, an abundant secretion of dilute urine may actually involve less work than a scantier flow containing the same total amount of solids.

In short, the work done by the kidney in the secretion of urine cannot be estimated at present either by the amount of the fluid or of its solid constituents, and there is no convincing evidence that during diuresis the renal cells are expending more energy than during moderate secretion.

Some years ago the measurement of the molecular and ionic concentration of the urine by means of its freezing-point was introduced as a clinical method of determining the efficiency of the kidney, and many references will be found to the procedure in the literature of the first decade of the century. Clinically the results have proved disappointing and misleading, and, in view of the considerations discussed in this chapter, there is no question that this "cryoscopic" method was much overvalued and has been abandoned rightly.

The earliest observation in regard to the metabolism of the kidney was that of Claude Bernard (1859), who states that during diuresis the blood of the renal vein is bright red, like that of the submaxillary vein during stimulation of the chorda tympani. Fleischhauer was unable to detect any such change in the colour of the blood during secretion, but observes that the blood of the renal vein is at all times redder than that of the vena cava. Loewi

(229), on the other hand, states that the venous blood coming from the kidney is distinctly brighter in colour in certain forms of diuresis. Another method was used by Grijns to demonstrate the activity of the kidney. He showed that the urine in the renal pelvis has a higher temperature than the arterial blood, and concludes that actual work is performed in secretion just as in muscular contraction.

More exact observations have been made by Barcroft with Brodie and other associates, who compared the gases of the arterial blood with those of the blood of the renal vein. They found that the kidney in normal conditions generally consumes more oxygen than the average tissues of the body, as is only to be expected, since among those tissues such inert substances as bone and fat have to be reckoned; but exceptionally, the oxidative processes in the kidney do not appear to be higher than in most other organs. In the dog, Barcroft and Brodie found the oxygen consumption to amount to 0·008-0·075 c.c. per gram per minute, while Bainbridge and Evans noted in an experiment in which the kidney was kept alive by a special method of perfusion, that each gram consumed 0·04 c.c. per minute.[1] In the rabbit, the average consumption is 0·082 per gram per minute (Tribe and Barcroft).

In some forms of diuresis the oxygen absorbed rises greatly, for example from 0·06 to 0·28 c.c. per gram per minute, and the total consumed by the kidney may form over 10 per cent of that taken up by the whole body.

The carbonic acid formed by the kidney varies more during rest, and does not show the same increase when its activity is heightened; it may, in fact, remain almost unchanged during active diuresis, though as a general rule some increase follows, and sometimes this may be almost as marked as that in the oxygen consumption. There is no measurable relation between the O_2 absorption and the CO_2 formation in the kidney in any period of time, nor can any definite ratio be made out between either of them and the amount of urine. This is in accord with

[1] Tangl has attempted to estimate the metabolism of the kidney by taking the O_2 consumption and CO_2 elimination in curarized dogs before and after excision of the kidney. By a very forced method of reasoning he concludes that his results agree with those of Brodie and Barcroft, but this will scarcely convince others; the uncontrolled factors in his method are too many to admit of accurate results.

the view discussed on p. 34, in which it is pointed out that the work done by the kidney is very imperfectly measured by the mere volume of the urine; not only the volume of the fluid, but the amount of the solids dissolved in it and the work done in separating these from the blood must be taken into consideration in this question.

When diuresis is caused by the intravenous injection of urea, sodium sulphate, or phlorhizin, there is always a marked increase in the oxygen absorption, but when the diuresis follows

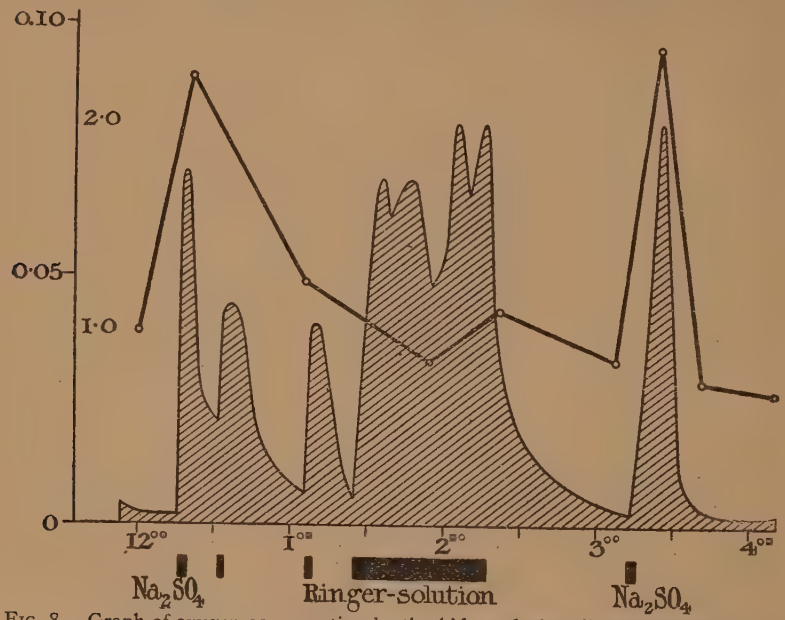

FIG. 8.—Graph of oxygen consumption by the kidney during diuresis (Barcroft and Straub). The black line represents the oxygen in c.c. taken up by each gramme of kidney per minute. The shaded areas denote the volume of urine secreted each minute. Time in half-hours.

the injection of water, Ringer's solution, or sodium chloride, it is often not accompanied by any such change in the metabolism (Barcroft and Straub).

In Fig. 8 the oxygen absorption is seen to rise during the diuresis caused by sodium sulphate, while during the interpolated diuresis from Ringer's solution no such increase is observed, although the secretion under Ringer's is greater than either of those under sulphate. And, curiously enough, it may be calculated from the figures given by the authors that the

amount of sulphate excreted during this Ringer's diuresis was actually greater than that during the second sulphate diuresis, though the percentage of sulphate in the urine was lower. This suggests that the oxygen absorption in sulphate diuresis is not the result of the sulphate excretion, but of some secondary result of this activity, possibly a change in the work of concentration. (See discussion in Chap. vi. *h*.)

The blood supply of the kidney is remarkably abundant, much more so than was believed by Heidenhain and the older writers on the subject.[1] Thus Tribe and Barcroft in a series of observations on the normal kidney of the rabbit found that on an average 2 c.c. of blood passed through the kidney per gram per minute. Dr. Barcroft informs me that in the cat about 30 c.c. of blood passes through the kidney per minute on an average, and this is perhaps too low rather than too high in my experience. In the dog, Barcroft and Brodie repeatedly observed a flow of 2 c.c. per gram per minute, and Burton-Opitz and Lucas, using a stromuhr method, found about 1·5 c.c. per gram per minute. All these observations thus agree fairly that the kidney is irrigated with nearly twice its weight of blood per minute. If the weight of the kidneys be taken at 0·8-0·9 per cent, and that of the whole blood at 7·5 per cent of the body weight, it may be calculated that the whole of the blood of the body passes through the kidneys in approximately five minutes. If this ratio holds in man, the blood-flow through the kidneys in twenty-four hours amounts to 1000-1500 litres. And even if the kidneys in man form only 0·4-0·5 per cent of the total body weight, as is often stated, the blood supply per day would exceed 700 litres; Metzner (1906, p. 241) estimates the blood supply in man from the calibre of the renal artery and calculates it at about 480 litres in 24 hours.

But this ratio varies greatly in different conditions; for example, in extreme constriction of the vessels the circulation in the kidney may cease altogether, while in other circumstances the rate of circulation may increase 50 or even 100 per cent.

[1] Even Landergren and Tigerstedt's estimate of $\frac{1}{4}$-$\frac{1}{2}$ c.c. per gram per minute is far below the truth, since their method (stromuhr with the use of peptone to prevent coagulation) must have interfered with the circulation more than they supposed. Under saline diuretics, however, they obtained 1·2 c.c. per gram per minute, though this also is below the true normal flow.

Nothing is known of the distribution of the blood in the kidney during such variations. The double capillary system gives large scope for variations in this respect, but it is not even known whether the efferent vessels of the glomerulus are controlled by nerves, much less under what conditions they vary in calibre.

In many forms of diuresis the blood circulating through the kidney is increased in amount, the vessels generally dilating. But this is not a necessary concomitant of an increase in the urine, as will be pointed out in a later chapter. An example of diuresis without change in the blood supply is offered under phlorhizin.

CHAPTER IV.

THEORIES OF RENAL SECRETION.

(1) *Bowman and Heidenhain.*

THE anatomical characteristics of the kidney have dominated the various views of its activity ever since Bowman (1842) first appreciated the relation of the Malpighian body to the system of tubules. The unique structure of the glomerulus and capsule suggested to him that here is the point at which the water of the urine is secreted, while the long and twisted tubule supplies the more characteristic solids, such as urea and uric acid. "It would be difficult to conceive a disposition of parts more calculated to favour the escape of water from the blood than that of the Malpighian body. . . . Why is so wonderful an apparatus placed at the extremity of each uriniferous tube if not to furnish water, to aid in the separation and solution of the urinous products from the epithelium of the tube." Bowman thus regarded the watery secretion as mainly a means of flushing out the tubules in which the urea, etc., were excreted in solid form. He, like many of his successors, does not state clearly where the ordinary salts of the urine are secreted, though he believes that "various foreign substances, particularly salts, which, when introduced into the blood, pass off by the urine with great freedom, exude in all probability through this bare system of capillaries" (i.e. through the glomerulus). Sugar and albumen also transude through the glomerulus, and blood cells may pass into the urine through rupture of the glomerular capillaries.

Bowman's theory remained without experimental evidence until 1874, when it evoked the powerful support of Heidenhain in two important investigations. These may be consulted for the details, but the most complete statement of the Bowman-Heidenhain view is given by Heidenhain in his article in Hermann's "Handbuch der Physiologie" (1883). The constituents

of the urine are secreted by the vital activity of the epithelium of the capsule and of the tubules. The glomerular capsule secretes water and "those salts which accompany water everywhere in the organism, such as sodium chloride," and, curiously enough, sugar in glycosuria and egg albumen. The epithelium of the convoluted tubules and of the wide part of Henle's loop eliminate most of the solids of the urine, including urea, uric acid, hippuric acid, pigment, hæmoglobin, and a considerable proportion of the salts. These are accompanied by a minimal amount of water under normal conditions, but in diuresis caused by urea or salts, the increased water also comes from the tubular epithelium and not from the glomerulus. In short, Heidenhain regards the glomerular capsule as normally secreting a dilute fluid apparently not far removed from a deproteinized lymph in constitution; this fluid as it passes down the tubules carries with it the products secreted by their walls, such as urea, uric acid, and salts, and issues in the collecting tubules as the normal urine.

If Heidenhain's view is interpreted in the terms of physical chemistry, as far as these are applicable, the capsule allows the diffusion into it of practically all the constituents of the plasma except the colloids and sugar; even the last is capable of permeating the capsule in diabetes. The epithelial cells of the tubules also allow the permeation of these constituents of the blood or urine, and differ from those of the capsule chiefly in the fact that less water ordinarily accompanies the solids. In both capsule and epithelium the diffusate from the plasma is driven onwards and expelled into the lumen by a special "vital" force. Heidenhain appears to have thought that the urea, etc., was actually concentrated in the epithelial cells, i.e. that a cell contained at any moment a larger amount of urea than a corresponding volume of plasma, but this does not seem essential to the theory; each molecule of urea may be conceived as carried through the cell immediately after its entrance (see p. 26), and this would correspond with the fact that the kidney contains very little urea (Cushny, 1917). The capsule and tubules thus differ only in degree of permeability, each allowing the entrance of all the constituents of the plasma except the proteins and sugar. When diuresis is excited by salts or urea, this difference in degree may apparently disappear, for now, under the stimulus of the salts, the tubules may actually allow the permeation of water

in larger quantity than the capsule. This tubular diuresis under salines is not discussed fully by Heidenhain, but it may be surmised that the salt normally permeates the cell along with a certain amount of water, and when the salt is present in excess, the water increases correspondingly; the cell in fact transmits the fluid of the plasma, perhaps in a concentrated condition, since it is more permeable by the solids than by the water. But it is difficult to imagine that very profuse diuresis could occur in this way. The saline diuresis is undoubtedly the weakest point of this view.

The activity of the glomerular capsule and that of the tubular epithelium are mutually independent, and each is subject to fluctuations of obscure origin. An important correlation is supplied by the blood-flow, for any change in its rate acts on both capsule and epithelium by altering the supply of material for each to work on, and also (and this Heidenhain appears to regard as more important) by influencing the supply of oxygen and the nutrition of the secreting cells.

Bowman's view of renal activity as elaborated by Heidenhain is attractive at first sight through its apparent simplicity. The kidney secretes urine, just as the submaxillary gland secretes saliva, except that certain cells have the function of removing the "specific urinary" constituents and any substance which is present in excess in the plasma. But closer examination shows that the behaviour of the kidney differs in almost all essentials from that of the typical secreting glands. Bowman based his view on the special anatomical feature of the kidney, the capsule, which he considered could only be adapted to the secretion of water, but Heidenhain removes the point of this argument by ascribing the secretion of water in diuresis to the tubules. The theory, in fact, gives no satisfactory account of diuresis, and in locating the secretion of water now in the capsule, now in the tubules, leads to constant confusion; for who shall say where the normal secretion from the glomerulus leaves off and diuresis from the tubules begins? Another grave objection to this view is that it endows the renal cell with powers of discrimination of a very high order. Not only is it able to distinguish foreign substances in the plasma from the ordinary constituents and to eliminate the intruders, but it is capable of detecting, and is aroused to activity by, quantitative aberrations in the composition

of the blood: thus sugar in 1 part per mille is indifferent to the renal cell, but when it rises to 2-3 per mille it arouses to activity a hitherto dormant function, that of secreting sugar.

The Bowman-Heidenhain theory, in fact, amounts to little more than the statement that the kidney secretes the urine by the vital activity of its cells. It has the advantage that no possible conjunction of conditions can be imagined which cannot be attributed to some special activity of unspecified cells, whose activity is governed by no known laws and whose anatomical position in the organ can be arranged to suit the circumstances. But such a nebulous statement of the renal function, while it offers a facile explanation of all possible observations, in reality explains nothing. As a defensive position it is impregnable, but it offers no point from which advance may be made. It may be necessary to retreat to it as a base if more adventurous theories are overthrown, but it would merely be a temporary position to be occupied until a more successful effort could be made to co-ordinate our knowledge of the activity of the kidney. The sterility of the view of specific secretion is shown by the fact that no significant advance has been made from Heidenhain's position of thirty years ago, and no attempt has been made to incorporate in his theory the new acquisitions from the study of physical chemistry. The advocates of specific secretion [1] have for the most part contented themselves with exhibiting the shortcomings and failures of other views of renal activity, without attempting to define more clearly their own position. It is true that they have sought to strengthen some of the foundations on which Heidenhain built, and the success attending their efforts will be discussed in later chapters. But every failure in the attempt to correlate an observation on renal secretion with other processes arising from the operation of known forces has been hailed as an argument in support of specific secretion, which really should be resorted to only when all other possible explanations can be definitely excluded, and this is seldom the case.

(2) *Ludwig.*

Two years after Bowman's view was published, Ludwig (1844) put forward another theory of the secretion of the urine, and it is interesting to find that he recognized at that time the defensive

[1] The best recent account is that given by Magnus (1909).

strength of Bowman's position. I translate freely one passage from his article: "To criticize Bowman's view it would be necessary to show that it is quite inadmissible on account of special features which mark the secretion of urine. But it is impossible to undertake this at the present time as resort can always be had to all sorts of subsidiary hypotheses." Ludwig held that the capsule was a simple filter, which allowed all the constituents of the plasma to pass through it except the proteins, and that in the tubules this filtrate was elaborated into the urine by the return of much of the fluid into the blood through a process of diffusion.

Ludwig, like Bowman, approached the problem of the kidney from the anatomical point of view, but he afterwards examined it experimentally. The best exposition of his position is given in his article in Wagner's "Handwörterbuch der Physiologie," 1844, and in his own "Lehrbuch der Physiologie," 1856, and second edition 1861. His later views were published not under his own name, but in the names of his pupils, Goll, Hermann, and Ustimowitsch, although much of the work was done by Ludwig himself.[1]

Ludwig's theory possesses only historical interest, no one at the present time supposing that the secretion of the urine can be explained by purely physical forces. At first (1844) he held that in the capsule the proteins were filtered off from the remaining constituents of the plasma, which were concentrated in the tubules by the diffusion of most of the water back into the blood. In this case the several solid constituents of the urine would bear the same proportions to each other as those of the plasma except for the proteins. In 1856 he recognizes this and explains the divergence in the proportions of the solids in the urine and plasma by supposing that some of the solutes in the glomerular filtrate may be absorbed more rapidly than others in the tubules; or, on the other hand, the constituents of the glomerular fluid may not be present in the same proportion as in the blood. Thus early, Ludwig is prepared to recant from glomerular filtration as filtration is now understood, or, as an alternative, to abandon absorption in the tubules as a simple diffusion, and accept differential absorption. In the second and last edition of his textbook (1861) he maintains the filtration and explains the change in the ratio of urea and chloride in the urine from that prevailing in the blood by supposing that the chloride permeates through the epithelium of the tubules more readily than the urea. The filtration and reabsorption are still for him simple physical processes. But in Ustimowitsch's research, performed in Ludwig's laboratory, a further factor in the secretion is recognized in the presence of urinary constituents in the blood; the greater the concentration of these, the greater the diuresis, and it is left open for future discussion whether these act through changing the permeability of the capsule or through effects in the tubules.

[1] See a historical review of the relations between Ludwig and his pupils by Sir Lauder Brunton (Proc. Roy. Soc. of Med. Therapeutic and Pharmacological Section, 5, p. 133 (1912)).

(3) *Modern Theory.*

The rival theories of Bowman and Ludwig have been the subject of constant discussion ever since they were brought forward, seventy years ago. Until Heidenhain developed Bowman's view, the ideas of Ludwig seem to have prevailed, but after that masterly piece of work appeared, they suffered an eclipse. More recently, the advances in physical chemistry of the last twenty-five years have finally disproved Ludwig's view by showing that the known physical forces are inadequate to form from the blood plasma a fluid of greater osmotic pressure (see p. 25). At the same time, the immobilizing effect of the uncompromising "vital secretion" of Heidenhain has been recognized, and emancipation has been sought in the gradual development of the modern view, which accepts the general scheme of filtration and reabsorption of Ludwig, but, appreciating the inadequacy of the known physical forces, supplements them as far as is necessary by the "vital activity" postulated by Heidenhain.

The energy supplied by the blood pressure, that is indirectly by the heart, is insufficient to perform the whole work of secretion, and the kidney must itself furnish the greater proportion of the energy required. The blood pressure in the glomerular capillaries suffices for filtration, however, and the capsule filters off the colloid substances of the blood plasma by which it is impermeable, while allowing the rest of the constituents to pass through without alteration in their relative concentrations (Tammann); the glomerular filtrate is thus practically deproteinized plasma. In its passage through the tubules this fluid is altered by the absorption of certain of its constituents by the epithelium; the passage of the absorbed water and solids of the glomerular filtrate through the epithelial layer entails the expenditure of energy by the cells; it is an active absorption, not the passive diffusion which was believed by Ludwig to be sufficient.

The secretion of the urine thus consists of two distinct processes differing not only in site but also in nature. The first of these, the filtration, occurs in the glomerulus, and is purely physical; the second, the reabsorption, occurs in the tubules, and depends on the vital activity of the epithelium.

Filtration through the renal capsule, like that through any

other membrane, such as ordinary filter paper, depends on several factors.

1. On the difference of pressure on the two sides of the membrane; this difference in pressure is supplied by gravity in ordinary filtration in the laboratory, in the kidney it is furnished by the blood pressure in the glomerular capillaries, which must always be higher than that in the fluid contained in the capsule if filtration is to go on.

2. On the character of the membrane. Different filter-papers vary in the amount of water which they allow to pass through per minute even if the pressure is the same; presumably they differ in the size and number of their pores. The renal capsule may show the same variability in different individuals, or even in the same individual at different times and under different conditions. Such alterations in the filtering capacity of the capsule would not of course change the filtrate in any way except in bulk. It would still remain identical with the plasma except in the colloid contents. But it is quite possible that with no change in the capillary pressure or in the constituents of the blood, the amount of the glomerular filtrate may change through changes in the capsule; a larger proportion of the fluid of the blood may thus escape at one time than at another. The filtration through the capsule changes when the supply of oxygen is insufficient, the resistance to the permeation obviously rising rapidly. In some pathological states a similar change in the rate of filtration occurs. The possibility of such a change in the filtering membrane does not seem to be appreciated by some critics of this view; an example of change of a similar nature is offered by the effects of alkali on filtration through parchment.

3. A third factor in the filtration is the nature of the fluid subjected to the process (the filtrand). In filtration through paper this factor hardly need be considered, because the pores in filter-paper are so large that everything passes through them that is not aggregated in comparatively large masses, and the rate of filtration remains uniform except in so far as these masses tend to choke the pores. It is quite different in the glomerular capsule, however, which allows molecules of small dimensions to pass freely, but retains the large molecules of the colloids. For while these are not in true solution, they exert a definite osmotic pressure and thus retard filtration. A simpler example of the

same phenomenon may be seen in the blood cell, which is practically impermeable by the sodium chloride of the plasma though it is freely permeable by the water; the chloride of the plasma, however, holds the water from entering the cell. In the same way the colloids of the plasma hold the water from passing through the glomerular capsule, into which they cannot themselves permeate. And this osmotic resistance offered by the proteins must be overcome by pressure on the fluid before any filtration can occur. The osmotic pressure of the colloids of blood serum was first determined by Starling (1899) at about 25-30 mm. of mercury, while Moore and Parker found 20-25 mm. and Moore and Roaf 30-34 mm. The colloids of plasma may thus be taken to oppose a resistance of about 30 mm. of mercury to their separation from the rest of the constituents of the plasma. Any change in the concentration of the colloids must alter this resistance, a more concentrated plasma offering a greater opposition, a less concentrated a smaller one. The osmotic resistance of the colloids has to be overcome by the blood pressure in the capillaries of the glomerulus if filtration is to occur, and the greater the concentration of colloid, the less filtrate will be formed at any given capillary pressure. Dilution of the blood plasma, in reducing the colloid concentration, increases the amount of the filtrate from the capsule (Starling).

Absorption.—The dilute glomerular filtrate which enters the tubules is very different from the urine which reaches the ureter. The latter contains a much higher percentage of small molecules and the proportions of the different solids have also changed, as is shown by comparing their concentration in the blood serum with that in the urine (p. 15). More than half of the water is probably absorbed even when a rapid secretion is proceeding, and in some cases more than 99 per cent of the water of the glomerular filtrate must be assumed to be reabsorbed in its passage through the tubules. This is shown by the change in the percentage of urea, which can hardly exceed 0·1 per cent in the glomerular filtrate, but which may reach 12 per cent in the urine of the cat; on the reabsorption theory, this can only be interpreted by supposing that 120 c.c. of the glomerular fluid containing 0·12 gram of urea loses 119 c.c. of water in passing along the tubules, leaving 1 c.c. containing 0·12 gram.

Some of the solid constituents are also absorbed by the

tubules, particularly the chlorides and sugar. Of the latter the whole must be taken up by the epithelium, for while it is present to the amount of 0·1 per cent in the fluid obtained by filtration from the glomerulus, only doubtful traces are found in the urine. In the above example, about 0·12 gram must have been contained in 120 c.c. of glomerular filtrate, and as none occurred in the urine, this must all have been absorbed. The chloride is also absorbed readily by the tubules; thus, 120 c.c. of glomerular filtrate would contain about 0·45 gram of Cl, while the 1 c.c. of urine only contained 0·00045, so that 99·9 per cent of that passing the capsule must have been taken up by the tubules. Sodium is absorbed in large quantity, potassium with difficulty (Bock), sulphates hardly at all, bromides as readily as chlorides. More water than chloride is generally taken up in the tubules, so that the urine contains a higher percentage of chloride than the plasma or the filtrate; but under special conditions, the chlorides may be present in the urine in lower percentage than in the serum, so that more of the salt is actually reabsorbed than of the water.

In short, the modern theory holds that the constituents of the plasma which I have termed Threshold Bodies (p. 22) are taken up by the cells of the tubules and return to the blood, while the No-threshold substances, such as urea, are rejected and can only escape by the ureter. Further, the threshold bodies are not absorbed indiscriminately but in definite proportions, which are determined by their normal values in the plasma; otherwise the kidney would eliminate waste products, but would fail to regulate the concentration of the threshold bodies in the plasma. The cells lining the tubules thus absorb from the glomerular filtrate a slightly alkaline fluid containing sugar, amino-acids and other similar food substances, and chloride, sodium, and potassium in approximately the proportions in which they are present in normal plasma, or in the artificial mixtures which have been introduced for the perfusion of surviving organs.

The function of the kidney may thus be shortly defined as the filtration of the non-colloid constituents through the capsule, and the absorption of "Locke's fluid" through the tubule cells. The capsule furnishes the tubules with the fluid as it exists in the circulation, the tubules return to the blood the fluid best adapted for the tissues, and allow the rest to escape in the urine. Thus if the plasma is too rich in sugar or chloride, the filtrate

also contains it above the threshold value; the epithelium, however, returns it at the optimal or threshold concentration and the remainder passes into the ureters. If much water has been ingested and the filtrate is correspondingly dilute, the subtraction of the optimal solution leaves the excess water in the urine along with the urea and other waste products.

The formation of the glomerular filtrate is due to a blind physical force, the absorption in the tubules is equally independent of any discrimination, for the fluid absorbed is always the same, whatever the needs of the organism at the moment. An example may serve to make this view clearer, and the analysis given on p. 15 may be taken, omitting the substances whose values have not been established (p. 18), and assuming that a litre of urine is formed. This urine contained 2 per cent of urea or 20 grams in all, and this was supplied from plasma containing only 0·03 per cent, so that $(\frac{20}{0{\cdot}03} =)$ 67 litres of plasma must have been drawn upon to furnish the litre of urine. The composition of the plasma and urine is given on p. 15, and that of the glomerular fluid and the reabsorbed fluid may be deduced as follows:—

	67 litres plasma contain		62 litres filtrate contain in all	61 litres reabsorbed fluid contain		1 litre urine contains	
	per Cent.	Total.		per Cent.	Total.	per Cent.	Total.
Water	92	62 l.	62 l.	—	61 l.	95	950 c.c.
Colloids	8	5360 gr.	—	—	—	—	—
Dextrose	0·1	67 gr.	67 gr.	0·11	67 gr.	—	—
Uric acid	0·002	1·3 ,,	1·3 ,,	0·0013	0·8 ,,	0·05	0·5 gr.
Sodium	0·3	200 ,,	200 ,,	0·32	196 ,,	0·35	3·5 ,,
Potassium	0·02	13·3 ,,	13·3 ,,	0·019	11·8 ,,	0·15	1·5 ,,
Chloride	0·37	248 ,,	248 ,,	0·40	242 ,,	0·6	6·0 ,,
Urea	0·03	20 ,,	20 ,,	—	—	2·0	2·0 ,,
Sulphate	0·003	1·8 ,,	1·8 ,,	—	—	0·18	1·8 ,,

The movement of the constituents of the plasma may be followed in their course through the kidney, the ultimate destination is indicated in the enclosures.

While the absorption of the optimal fluid is due to unknown

forces and cannot be further analysed, it is permissible to consider what factors may change its extent.

1. The absorbing power of the cells may possibly be increased or decreased by drugs just as a nerve cell may be stimulated or depressed. As yet this has not been demonstrated for the absorption as a whole, though there is reason to suppose that certain constituents of the filtrate are not reabsorbed in the presence of some poisons (see Phlorhizin).

2. The presence of any unabsorbable substance in the fluid passing along the tubules limits the absorption, for it offers osmotic resistance which increases as the fluid is taken up until it can no longer be overcome by the cell activity. The most important normal constituent which limits absorption in this way is the urea, but sulphates and phosphates also play their part. The threshold bodies which are ordinarily taken up by the epithelium may act in this way if they are present in such quantity in the filtrate that the water is not sufficient to form the dilute optimal solution. Thus sugar if more concentrated in the filtrate than 0·2-0·3 per cent, is not all absorbed, and the excess retains water in exactly the same way as a no-threshold body like urea.

The urine can therefore never exceed a certain concentration, at which the osmotic resistance is equal to the power of absorption. This differs in different animals, the cat being able to absorb against a resistance of at least 50-60 atmospheres, while the dog is less efficient; the human kidney is probably inferior to both of these, though it is said to be able to concentrate sugar to 20 per cent, which would exert a resistance of nearly 25 atmospheres. The lowest power of concentration is probably that of the rabbit, and this is of importance, as so much of the experimental work on the kidney has been carried out on these animals.

3. The amount of absorption must depend to a certain extent on the time during which the filtrate remains in contact with the cells, that is, upon the rate at which it passes along the tubules. When the filtrate is abundant and flows rapidly through the tubules, the absorption is less complete than when it remains for some time in the tubules. The urine may therefore be expected to be less changed from the original filtrate when it is abundant, that is, it will resemble deproteinized serum more closely than when it is less abundant. And this is generally

found to be the case. But even when maximal diuresis occurs, a certain amount of absorption must be accepted. For even when as much as 5 c.c. of urine was being secreted per minute by a small rabbit, it contained 0·26 per cent of sulphate, while the serum had 0·15 per cent; this increase in the sulphate concentration indicates that each 100 c.c. of water filtered by the capsule lost more than 40 c.c. in its passage through the tubules. This failure of absorption from overflooding is especially liable to occur in the rabbit in which absorption is peculiarly ineffective at the best; it is naturally more prone to occur in any animal when a copious intravenous injection is made than when fluid is absorbed from the tissues or from the alimentary tract. In fact, doubt may be entertained whether the absorption is ever greatly impaired by flooding except under intravenous injection.

4. It has been suggested by Loewi (225) that the absorption of any constituent from the filtrate may be retarded by its presence in abnormal concentration in the lymph and blood. For example, if sugar is abundant in the plasma, the cell would find greater osmotic resistance to the extrusion into it of a molecule absorbed from the filtrate. This is no doubt true theoretically, but its practical effect need not be taken into consideration; for even if the sugar amounted to 0·5 per cent in the plasma it would exert an osmotic resistance of about 0·62 atmosphere, and this can hardly cause any significant change in the working of a cell which is accustomed to overcome a resistance of at least 20-30 atmospheres at its other pole.

The filtration through the capsule and the reabsorption in the tubules are independent processes, but are co-ordinated in some measure by the common blood supply; for an increase in the blood-flow through the capsule favours filtration and at the same time increases the blood supply to the tubules and therefore may augment the activity of the epithelial cells. A further correlation has been mentioned already; the larger the filtrate, the more rapidly it passes through the tubules and the less favourable the conditions for reabsorption. This second correlating factor must thus tend to diminish the importance of the first.

General Consideration of the Bowman-Heidenhain and the Modern Theories.

The two leading theories of renal secretion agree in locating the secretion of water in the glomerular capsule at any rate for the most part. And, in fact, they do not differ fundamentally

in their conceptions of the function of the capsule. The one regards mechanical filtration as sufficient to explain the glomerular fluid, while Heidenhain held it to be insufficient and therefore contended for further unknown, or vital, activities. But both schools agree fairly satisfactorily that the fluid is of the nature of a deproteinized plasma as a general rule. A more marked divergence exists as to the quantity of the glomerular fluid, for while Heidenhain supposes this to be approximately that of the urine, the modern view requires a vastly greater amount of fluid, since it has to supply not only the water of the urine, but the whole of the solids also.

In regard to the tubular epithelium the two views are diametrically opposed, the later ascribing to it merely the function of absorption, while Heidenhain held that it is primarily secretory, though he conceded that under exceptional conditions it may absorb fluid from the tubules to some extent. The problem here is therefore to determine the direction of the current in the epithelium. Does it set towards the lumen of the tubule, as Heidenhain supposed, or away from the lumen, as Ludwig suggested?

Many attempts have been made to make the best of both theories. For example, a compromise has been suggested by which filtration is accepted in the capsule, but the tubules are regarded as purely secretory in function. The fatal objection to this suggestion is that the glomerular fluid, if a filtrate, must contain about 0·1 per cent of sugar, while the normal urine is sugar-free. Similarly, the glomerular filtrate must contain about 0·3-0·4 per cent of chloride, but the urine may contain only a trace sometimes. Any view that includes filtration in the capsule, as a significant factor in the formation of urine, must entail subsequent absorption in the tubules, a sequence that seems to have escaped many recent writers on the kidney.

A still more catholic view (Metzner, 1906) would accept filtration in the capsule and reabsorption in the tubules, but postulates in addition that some parts of the tubules are also secretory in function. In support of this, the histologists point out that the structure of the convoluted tubules suggests that they are secretory in function, while the low epithelium of part of the loop of Henle may well be adapted to absorb superfluous fluid; but to this argument it may be objected that the latest

writer on the histology of the tubules, Suzuki, limits secretion to the proximal convoluted tubules, while at the same time he holds that the non-secretory distal convoluted tubules resemble the proximal secretory ones so closely in appearance that most of his precursors have failed to distinguish between them; this appears to weaken the histological argument. Apart from this, however, this compromise is certainly comprehensive enough to include all the known phenomena of renal secretion, and it may be necessary to supplement what I have termed the modern view with an active secretion in the tubules. But it should be held in reserve, to be invoked only if the simpler view proves to be insufficient; and perhaps not even if it fails in obscure and occasional cases, but only if it fails all along the line.

Loewi (225) has attempted to unite the secretion of Heidenhain with the filtration of Ludwig in a theory which has received more attention than its intrinsic value would seem to merit. He accepts the filtration of all the non-colloidal constituents of the plasma, but holds that phosphate and sugar circulate in the blood in colloid combinations and that they can only be eliminated by the kidney by active secretion of the epithelium of the tubules; but the whole basis of his argument is fallacious, for both the sugar and phosphate occur free in the plasma, as is shown by their diffusing through dialyser membranes.

A Priori Considerations.

The arguments in favour of one or other of these views have occupied experimental investigators for many years. Some authorities deprecate what they regard as the excessive attention paid to this problem. But no satisfactory progress can be made in the physiology of the kidney until some agreement is reached in this fundamental question. And since many of its aspects appear to have received insufficient attention hitherto, it will occupy a certain part of the following pages.

Before entering on the experimental observations, it may be well to discuss some arguments of an *a priori* character which have been urged against the filtration-reabsorption view, and which have received greater attention than they deserve. And first it is "contrary to common sense" that the kidney should first "excrete" a large amount of fluid in the capsule and then forthwith proceed to reabsorb it in the tubules. But this is, on the contrary, a common phenomenon in the body. All along the

alimentary tract and elsewhere, quantities of fluid are constantly being shed out at one point only to be reabsorbed lower down. The best example, perhaps, is the liver, which throws into the duodenum 500 c.c. of fluid in twenty-four hours, all of which is reabsorbed in the bowel, except some pigment. It may be objected that the bile is excreted to supply the bowel with bile-salts and alkali, and that fluid and salts are reabsorbed after they have fulfilled their function; but much more fluid is secreted than is necessary to dissolve these necessary constituents. I do not wish to drive an analogy to extremity, but the argument applies equally to liver and kidney. A more cogent argument is the absorption of the urine itself in the birds; in these the urine passes down the ureter as an abundant and generally clear fluid, but in the bowel the water is almost all absorbed, leaving a thick paste of urate (Sharpe, 1912). Here there can be no question that reabsorption occurs, and although there is a special mechanism apart from the kidney, the analogy is sufficiently striking. There is, of course, in addition to this reabsorption in the intestine, a preliminary stage of reabsorption in the kidneys according to the modern view. The bowel only completes the process begun in the renal tubules.

A further criticism was urged by Heidenhain and has apparently carried great weight: In man about 35 grams of urea are excreted in twenty-four hours (a rather high estimate), while the blood contains about 0·025 per cent of urea. He calculates on a basis of 0·05 per cent in the glomerular filtrate that no less than 70 litres of filtrate must pass the capsule per day to supply the 35 grams of urea in the urine. On the other hand, the total urine in twenty-four hours only amounts at the most to 2 litres, so that of the 70 litres no less than 68 litres must be absorbed in the tubules if the urine is formed from the glomerular filtrate by reabsorption. The alternative view of Bowman and Heidenhain, it may be added, requires that about 68 litres of plasma shall exude into the lymph spaces around the tubules to permit the urea to pass into the secretory cells. The two rival theories, in fact, both require about the same amount of fluid to come in contact with the epithelium, but according to Ludwig the fluid reaches the cells from the interior of the tubules and is absorbed, while according to Heidenhain it merely flows along the base of the cells and gives up its urea to them and is then reabsorbed by

the lymph and blood vessels. The difficulty is almost equally great in accepting either theory.

Heidenhain's figures are certainly striking, and his argument has been sufficient to prejudice superficial readers against the theory he attacks. Let us analyse them a little further, or rather let us examine the same problem in the cat, in which more details are ascertainable than in man. A cat fed on meat only passed on an average 100 c.c. of urine per day containing 12 per cent of urea. The blood-flow through the kidneys, measured by Barcroft and Brodie's method, amounted to 40 c.c. per minute, and the blood contained 0·1 per cent of urea; that is, the 100 c.c. of urine contained as much urea as 12 litres of plasma. The modern view demands that 12 litres of fluid were filtered through the capsules, and that no less than 11·9 litres were reabsorbed in the tubules, much higher figures in proportion to the relative weights of the cat and man than are calculated by Heidenhain. Each kidney of the cat contains about 16,000 glomeruli and tubules, so that the amount of fluid filtered by each glomerulus in the twenty-four hours in my observation was ($\frac{12000}{32000}$ c.c. =) 0·375 c.c., or on the average about 0·015 c.c. per hour. Of this more than 0·014 c.c. was absorbed in its passage along about 3 cm. of tubule, leaving less than 1 mg. per hour from each capsule to finally enter the collecting tubule. When the immense number of tubules in the kidney is taken into account, the argument of Heidenhain is thus seen not to be so fatal as has been supposed, for 0·015 c.c. per hour cannot be regarded as a very severe task for the capsule, and the absorption of 0·014 c.c. of water per hour would seem to be well within the capacity of the epithelium of a tubule 3 cm. in length.

Further calculation of this experiment shows that if the blood-flow may be taken as unchanged during anæsthesia, nearly 60 litres of blood passed through the kidneys of the cat in twenty-four hours, containing about 35 litres of plasma. Of this, 12 litres were filtered off by the capsule, and 11·9 were restored by the tubules. Heidenhain based some further objections on a much too low estimate of the blood supply of the kidney.

Heidenhain's argument has also been used by Bock (1907) who estimated the amount of potassium in the blood and urine of rabbits during a moderate diuresis, and calculated that the glomerular filtrate must amount to nearly 16 c.c. per minute, and that of this more than 15 c.c. were absorbed in the tubules. If the rabbit is credited with approximately the same number of

glomeruli as the cat, Bock's observation would imply that each capsule filtered about 0·5 mg. of fluid per minute during moderate diuresis, and that about 0·45 mg. was absorbed in its passage through a 3 cm. tubule ; this does not seem to demand any incredible activity on the part of the capsule or of the tubules.

Another argument of essentially the same nature is cited from the occurrence of very dilute urine after copious draughts of water. One of the most striking examples is that given by Macallum and Benson, who found that after copious water-drinking 205 c.c. of urine was secreted in ten minutes, and that the concentration was only about one-eighth of that of the blood (Δ of urine = $-0{\cdot}075°$, Δ of blood = $-0{\cdot}56°$). Here about 20 c.c. of urine was passed per minute by human kidneys, which have been estimated to contain together from two to four million glomeruli. Taking the lower number, each tubule emitted 0·01 mg. of urine per minute, and if the glomerular filtrate be taken at 0·05 mg. per minute, the rate of secretion and of re-absorption cannot be regarded as beyond conception.

And the same considerations dispose of similar experiments cited by others. The objection to filtration and reabsorption disappears when the enormous number of the filters and the large absorbing surface is appreciated.

Hill and Filehne and Biberfeld (115) have argued from physical considerations that filtration is impossible because the cell substance, being practically a colloidal solution, must transmit pressure equally in all directions; the fluid in the capsule must therefore be under the same pressure as that in the glomerular capillaries. The answer to this objection is given by the facts that filtration occurs through gelatin, and also in the dead kidney perfused with saline solution (Sollmann).

The chief attraction of the original Ludwig theory lay in its eliminating altogether the unknown vital activity of the cell. The modern theory accepts this activity as necessary, and it may be asked wherein it can claim preference over the Bowman-Heidenhain view. It is true that in essential features it is fairly simple, but in detail it bristles with complications and difficulties, which are at any rate not so obvious in the straightforward statement that the urine is secreted like the saliva. The chief advantage of the modern view is that it reduces the kidney to a machine instead of postulating for it the capacity of a highly

trained analytical chemist. One part of the kidney filters off the plasma colloids, another part absorbs a fluid of unchanging composition. The kidney exercises no discrimination, but continues these activities through life, just as a muscle exercises no discrimination. The kidney loses somewhat in dignity and romance when it is thus represented as merely a hard-working organ, which is admirably fitted to remove the waste products of the blood, but which is so devoid of judgment that in some conditions it acts to the prejudice of the organism by removing the diluent instead of the poison. And the complications and difficulties of the modern view arise from its attempt to take cognizance of the intricate conditions under which the organ functions. The kidney does not behave to changes in the pressure or the composition of the blood in the same way as the salivary gland, any more than it resembles it in its structure, and no theory of the secretion of the urine can be considered satisfactory unless it recognizes these essential differences.

The modern view dispenses with the power of the kidney to discriminate between minute changes in the composition of the blood, and this renders it superior to the rival view of specific secretion. It is impossible at present to prove it correct, but this is unnecessary. It is sufficient to show that it is in accordance with a large body of observations. Even if it fails to offer complete explanation of these, it merely requires further development, not abandonment.

The Propulsor Theories of the Glomerulus.

According to the view of Heidenhain, the functions of the glomerulus and the tubules are essentially of the same order; the one may secrete more, the other less, of any one constituent, but both secrete water and salts and perhaps urea. This, however, appears to be difficult to reconcile with the great difference in their anatomical appearance. If the function of the glomerulus is simple secretion, like the tubules, or the sweat glands, or salivary glands, how is the development of this very special apparatus to be accounted for? Strict logicians have therefore attempted to find a new function for the glomerulus. Thus Lamy and Mayer (206, p. 660) suggest that its main function is not to secrete fluid itself, but to drive forward the urine secreted in the tubules. They regard the glomerular tuft as a sort of piston, which is alternately enlarged and retracted by the pulsations of the heart, and which thus pumps the fluid of the tubules onwards. The chief arguments in support are drawn from the observations of Huot and of Regaud and Policarde, who found that in some of the fishes the kidney had no glomeruli at all,

or only one glomerulus for several tubules. These arguments do not appear convincing, and these authors have forgotten that a pump must have inelastic walls and a valve as well as a piston, while the walls of the tubules cannot be said to be rigid, nor is there any valve in the kidney; the pulsation of the glomerulus in itself can only cause a slight to-and-fro oscillation of the column of fluid and no propulsion. A view somewhat similar to that of Lamy and Mayer seems to have been propounded by Smith many years previously (see Brodie, 1914). Brodie (1914) holds that the pulsation of the glomerulus has little bearing on the flow of the urine along the tubules, and points out that when the excised kidney is perfused with a constant stream, fluid escapes freely from the ureter. He regards the glomerular capsule as a secreting surface, but considers that the characteristic form enables it to set up a "pressure-head" sufficient to drive the secretion along the tubule. By measurements of the calibre of the tubules and calculations according to Poisseuille's law for the passage of fluids along narrow tubes, he reckons the pressure necessary to drive the fluid along the tubules and finds it comparable to that existing in the glomerular capillaries. I must admit that I have difficulty in understanding the view of this author as to the relation between the pressure in the capillaries and that in the interior of the capsule. For a steady pressure in the former can be transmitted to the latter only if the fluid is forced through the capsule by that pressure; if a surface allows the passage of fluid or even secretes it actively, the neighbourhood of an object in which a high pressure is maintained can have no influence on it unless the fluid escapes under that pressure; the passage of a railway train at high speed does not affect the flow of the river under the bridge. Unless the pressure in the capillaries determines the rate of flow through the membrane, it cannot influence the pressure in the interior of the capsule; but this is filtration, and to Brodie filtration is anathema.

As regards the application of Poisseuille's law to the movement of the fluid along the tubules, it may be pointed out that the measurements of their calibre have necessarily been made on hardened sections, and some doubt may be entertained as to how far these represent the values in the living kidney. But if Brodie's figures for these be accepted as correct, a pressure of about 80 mm. of mercury is required to overcome the resistance of the tubules to the passage of fluid at the rate of 1 c.c. per minute. Now one of the few points on which there is no dispute, is that urine can be secreted at a blood pressure of 40 mm. of mercury; the secretion may be smaller or greater than that observed by Brodie, and the resistance to be overcome in its passage must thus rise above or fall below that calculated by him. Again when the dead, excised kidney is perfused at 20-25 cm. water pressure (= 15-20 mm. Hg), fluid escapes from the ureter in some quantity. This is quite impossible on his calculations of the flow of liquids along tubes. It may well be questioned whether Poisseuille's law holds for the passage of fluid along non-rigid tubes of the calibre of the renal tubules and at the extemely slow speed (p. 54) which prevails there. So far as I can find, this has not been examined by physicists.

CHAPTER V.

DIRECT EVIDENCE ON THE FUNCTIONS OF THE TUBULES AND GLOMERULUS.

Secretion of dyes—of salts—of uric acid—of calcium, phosphate, and iron—of chlorides, sugar, and urea.

(*a*) *Secretion of Dyes.*

THE most impressive argument in favour of secretion by the tubules is that given by Heidenhain's (1874) experiments with sodium sulphindigotate (indigosulphonate, indigocarmine).[1] The spinal cord was divided in a series of rabbits in order to reduce the blood pressure and the secretion of urine, and a saturated solution (about 1 per cent) of sodium sulphindigotate was injected intravenously. If the animal was killed in about ten minutes, the cells of the tubules were found stained blue (Fig. 9 A), while if it was allowed to survive about an hour, the cells were colourless and the pigment lay in masses in the convoluted tubules and the wide part of Henle's loop (Fig. 9 B). No urine was passed in either case, and the capsule remained colourless. Heidenhain therefore believed that the pigment is taken up from the blood and lymph by the epithelial cells of the tubules, which excrete it into the lumen, and that this excretion occurs in the absence of glomerular activity and without the secretion of urine.[1] In fact, if the capsule is active, as in rabbits with uncut spinal cord, the appearance of the kidney is quite different, as the pigment is swept away from the convoluted tubules and appears in the collecting tubules and eventually in the ureter and bladder.

[1] If the circulation of part of the kidney is impaired by applying caustic silver to one point of the cortex before the dye is injected, the segment beneath the injured zone shows the same appearance—the indigo is precipitated in masses in the convoluted tubules—while in the rest of the organ it has been swept further downwards by the secretion of the glomeruli. Kabrhel attempted to confirm this observation in the rabbit's kidney by removing

part of the cortex by the knife, but the subsequent injection of indigo gave the same appearances in the affected segment as those presented by a dead kidney injected with indigo by the renal artery.

Heidenhain's presentation of this argument (1883) is so clear and cogent that it has frequently been accepted as a final proof of the secretion of indigotate by the tubular epithelium, and too little attention has been paid to the criticisms which have been made by many subsequent investigators. Those who followed Heidenhain's directions implicitly, appear to have had no difficulty in obtaining the general features of the histological picture he describes (Höber (1905), Basler (1906), Schafer (1908)), though some details may have been different. And many accept his interpretation of the results of these experiments, but an alternative has been proposed by Sobieranski (346), who suggests that the indigotate is really eliminated by the capsule in a very dilute solution, and passing into the tubules is there concentrated by the absorption of water until it is finally precipitated in masses in the lumen; the coloration of the epithelium is explained not by the dye passing through it towards the lumen, but by small quantities being absorbed from the lumen by the cells.

FIG. 9.—Renal tubules after sulphindigotate injection (after Heidenhain's description). A, early stage with diffuse coloration of the cells and nuclear staining. B, later stage with the granules of indigotate in the lumen of the tubules.

Heidenhain was quite prepared for this interpretation of his observations, and considered that his methods excluded it. It remains to consider how far his precautions were effectual. His argument consists of three parts: firstly, the glomeruli were uncoloured and therefore the dye could not have passed through them; secondly, the epithelial cells were stained and therefore were excreting the dye; thirdly, the dye appeared in masses in the tubules when time was allowed for the excretion to be completed.

As regards the first point, absence of stain in the capsule, this was the case in the majority of his experiments, and Schafer (1908) never observed any coloration, though the latter's state-

ment is weakened by the addition that the cells of the convoluted tubules were also only slightly coloured. But the absence of stain in the capsule in many experiments may be explained by the suggestion of Nussbaum (1878), that the dye may pass through the capsule in such a dilute form as not to stain it, or possibly in a reduced and colourless form; in support of this he points out that in the liver the bile capillaries are full of indigotate, yet the cells through which it must have passed are colourless. And even in the kidney itself the tubules are often unstained though the urine is blue, showing that when indigo passes through in sufficiently dilute solution it fails to colour the cells by which it is excreted (Kabrhel). Further, while Nussbaum confirms Heidenhain's experiments in the mammal, he states that in birds, fishes, and amphibia the dye is found in the lumen of the tubules but occurs neither in the capsule nor in the interior of the cells of the tubules; this has been confirmed by several later observers (Gurwitsch). Kabrhel (1886) states that in the frog indigo may be observed in quantity in the lymph spaces and subsequently in the lumen, but he could not find it in the cells, though the basal membrane was sometimes coloured.

Other observers have laid emphasis upon the fact that while in some experiments the capsule is unstained by indigotate, in others its cells show a diffuse coloration from it, and in still others the dye may be found in masses in the lumen of the capsule (Fig. 10). The capsule was observed to be coloured by Heidenhain in some cases, and Pautynski (1880) noted this generally in his experiments, which, however, are invalidated by the huge amount of fluid and dye injected. But Henschen (1879) and Sobieranski (1895) on repeating Heidenhain's experiments on rabbits with section of the spinal cord and injection of small quantities of indigotate, found that not only was the glomerular capsule stained blue, but masses of precipitated indigo could be observed in the lumen of the capsule (Fig. 10); this picture was obtained only when the animal was killed within one or two minutes after the injection; later the colour disappeared from the capsule, and the

FIG. 10.—Coloration of glomerulus and deposit of indigotate in the capsule after the injection of indigotate (after Grützner).

tubule cells, which were previously unstained, now presented the appearance described by Heidenhain. The observations of Henschen are confirmed by Grützner (1881), whose admissions are of the greater weight because he is a devoted adherent of Heidenhain's views. It is true that he attempts to explain away Henschen's and his own results as being pathological rather than physiological, but the experiments appear to have been done in exactly the same way as the original ones of Heidenhain, so that his criticism embraces not only those of Henschen but also those on which the whole theory is founded.

Heidenhain did not depend solely on the fact that the capsule was unstained however, but attempted to eliminate the glomerular activity by cutting the spinal cord in order to reduce the blood pressure to a point at which no urine could be secreted ; it is true that he gives no actual figures for the blood pressure and only measured the urine in the bladder. And it is objected that the failure of urine to reach the ureter is no absolute proof that no fluid left the capsule, for it is possible that the whole of it was absorbed in its passage down the tubules, leaving the indigo behind in the lumen. This argument, little plausible though it may seem at first sight, cannot be brushed aside without further consideration and is not met by Heidenhain's precautions.

Thus it cannot be asserted that Heidenhain's method excludes the possibility that the deposits of indigotate in the tubules may be derived from a dilute solution escaping from the capsule. Further light is thrown on the question by observations made with carmine injections (carminate of sodium, ammonium, or lithium). Chrzonsczewski (1864) and Wittich (1875) found that in rabbits injected with carmine the capsule was stained a diffuse red and some of the stain was contained in its lumen ; large quantities were seen in the lumen of the contorted tubules, and the inner margin of their epithelium was stained red while the body of the cell was colourless. They concluded that carmine is excreted by the capsule and not by the tubules, and this was accepted by Heidenhain (1883). Later observers (Schmidt (1891), Ribbert (1894), Sobieranski (1895), Basler (1906)) confirm in most points the earlier investigators, though the stained granules are not always confined to the internal striated border of the cells. It is clear that carmine stains the capsule more

readily than indigo, and it is suggestive that the former is not reduced by the tissues, while the indigo is readily reduced and decolorized and as readily recovers its colour. It is possible, therefore, that, as Nussbaum suggests, the difficulty in staining the capsule with indigo may arise from part of this dye passing through it in a reduced form and then recovering its colour in the tubules; this view is confirmed by the observation of Schafer (1908) that reduced indigotate becomes coloured in the convoluted tubules. Apart from the fact that the capsule is readily stained with carmine while it is often unstained by indigo, the behaviour of these dyes in the kidney is very similar, as was pointed out by Schmidt in Heidenhain's laboratory.

Turning now to the second of Heidenhain's points, that the presence of the stain in the cells of the tubules indicates that it is being excreted by them, we find again some modification necessary in the light of later observations. According to Heidenhain's statement, the cells are diffusely stained with indigotate, the nuclei containing rather more of the dye. But this diffuse and nuclear staining is generally considered to indicate that the dye penetrated the cells only after death (Schlecht, 1907). And it has therefore been suggested that the staining in Heidenhain's experiments was *post-mortem*, from the diffusion of the stain from the lumen of the tubules; Heidenhain believed that he had excluded this by washing out the kidney with alcohol, but this is not sufficient to precipitate the whole of the dye in the tubules. Schafer (1908) states that he never obtained staining of the epithelium without the presence of granules in the lumen, so that he is unable to confirm Heidenhain's description of the early stage, and Jacobj and Sobieranski obtained the same histological picture as Heidenhain from an excised dog's kidney perfused with indigotate, although there can be no question that the organ was dead.

The characteristic of *intra vitam* staining, such as Heidenhain attempted, is the deposit of the dye on the intracellular granules, which stand out in contrast to the uncoloured background of protoplasm and nucleus. This has been observed in the kidney under sulphindigotate by Arnold, and under other stains by many observers (Fig. 11). Under carmine the granular staining is readily obtained and has been frequently followed, and the results throw a very interesting light on Heidenhain's interpretation.

Basler pointed out that the urine may contain the dye before any coloration of the tubules can be made out, though the glomerulus is deeply stained; and he inferred that carmine is excreted in part by the capsule. Heidenhain had previously noted that in uninjured rabbits indigotate appears in the urine without staining the tubules, and concluded that it was washed out too rapidly, but this can hardly be the explanation under carmine, when it stains the capsule and not the tubules. And Suzuki has extended Basler's statement by showing that masses of carmine are present in the lumen of the lower segments of the tubules before any significant staining of the granules in the cells of the convoluted segment is present. On the other hand,

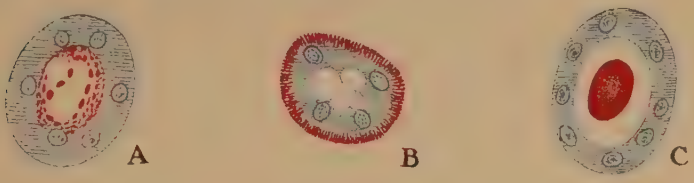

FIG. 11.—Carmine in the tubules. A, early stage in which particles of the dye are seen in the lumen of the convoluted tubules before the cells are stained. C, a mass of carmine (cast) in a collecting tubule at this stage. B, the late stage, in which the cell-granules of the convoluted tubules are deeply stained, but the dye has disappeared from the lumen (modified from Suzuki's figures).

this granular staining is present for days or even weeks after the carmine has disappeared from the urine. As Aschoff says, the elimination of the dye in the urine reaches its highest point from a few minutes up to an hour after the injection, while the accumulation of dye in the granules is greatest in twelve to twenty-four hours. It is obvious therefore that the granule staining in the convoluted tubules (and here alone is carmine found in the interior of the cells) "has nothing to do with the secretion of the dye" (Suzuki), but is a feature which these cells share with many others, such as those of the spleen, which have no excretory power whatever. The granules are of course not formed of carmine, as was formerly supposed, but are the normal cell granules stained with it.[1]

[1] The granules in the lumen of the tubules have very frequently been held to be identical with those in the interior of the lining cells, and curious theories have been suggested for their escape from the cells into the lumen; there is no longer

With this falls the chief prop on which Heidenhain's argument rests. But Basler and Suzuki both hold that while carmine is excreted by the glomerulus in large part, some escapes through the cells of the convoluted tubules. Suzuki bases this view on the occurrence of carmine granules in the cells close to the striated border when large amounts of carmine are injected; but this deposit may equally arise by absorption from the lumen as from its deposit in the course of its passage from the blood; the fact that these granules may appear before the dye has accumulated in the cell in sufficient quantity to stain the larger cell granules, may be cited in support of this view. It may be asked why the cells should absorb a useless pigment, but it is to be remarked that they are no longer quite normal at this stage, for Suzuki finds various signs that carmine injures the cells in its passage through the kidney.

In regard to Heidenhain's third point, the accumulation of masses of dye in the tubules, it was remarked by him, and is confirmed by most others, that these masses are much larger and more compact in the lower segments of the tubules than in the upper. Heidenhain explained this by supposing that the salts, which he supposed to be excreted by the tubules, render the indigotate less soluble and thus increase the deposit. But even on the assumption that salts are excreted by the tubules, this view cannot explain the increasing masses of carmine and other dyes, which are not precipitated by the salts of the urine. The growth of these masses can be explained only by an increase in the concentration of the dyes as the fluid passes down the tubule, and this concentration does not arise from their secretion in the lower segments, for Suzuki showed that the dyes occur only in the cells of the proximal convoluted tubules. Yet larger granules are present in the collecting tubules than in the loop of Henle, and this can only mean, as Ribbert first pointed out, that some of the fluid is absorbed in its passage downwards through the tubules.

Ribbert (1894) injected a mixture of carmine, indigotate and urate, and found all three in the lumen of the convoluted tubules, one of them predominating in one tubule, another in another. When carmine was injected along with hæmoglobin or egg albu-

room for doubt that the masses in the cells are merely the normal granules stained with the dye, while those in the lumen consist of dye in a fairly pure condition. (See Schlecht for discussion.)

men, the carmine appeared in the tubules, while the proteins extended into the capsule, but this difference may arise from the carmine being eliminated more rapidly than the proteins.

Many other dyes have been used for "vital staining," and have all proved to give similar results to those of indigotate and carmine. Dreser's experiments with acid fuchsin will be discussed in the chapter on the acidity of the urine. Arnold (1902), Gurwitsch (1902), Basler (1906), Höber and his pupils (1905, 1908), and Schafer (1908) have examined a large series, some of which resemble carmine in colouring the capsule more readily than the tubules, while others, like indigotate, often leave the capsule and glomerulus uncoloured while they accumulate in masses in the tubules. Gurwitsch draws further attention to the accumulation of these dyes in the epithelial cells of the tubules, enclosed in vacuoles or deposited on granules, and assumes from an unsatisfactory method of experimentation (see p. 79) that these vacuoles are specially adapted to collect or condense the dyes and carry them through the cells from the lymph to the lumen. He further discriminates between several types of vacuoles, one being utilized for the transport of lipoid-soluble dyes, another for those insoluble in lipoids, and a third for uric acid. Höber and Königsberg found, however, that the same "vacuole" may contain both kinds of dyes, and thus dispose of Gurwitsch's elaborate theory (see also p. 29). Höber and Kempner state that the dyes insoluble in lipoids are excreted chiefly by the second segment of the tubules in the frog, while the lipoid-soluble ones permeate all the tubule cells indifferently. The more colloidal the nature of the dye the less tendency has it to enter the cells.

Finally, a curious experiment performed by Ghiron (1913) has to be mentioned here. He put the living kidney of a mouse under the microscope and watched the changes following the injection of dyes given intravenously. The part focussed is the convoluted tubule, and he describes how the dye is first seen in the lumen, then spreads over the whole cell, and then fades slowly from the lumen to the base. After section of the cervical cord the stain does not appear in the tubule, but if dye is injected along with urea, the tubule presents the same series of pictures as in normal animals. Ghiron holds that his observations support the view that the dyes are secreted by the glomerulus and reabsorbed from the tubules, and if his experiments are confirmed they will certainly tend to do so. It is obvious that confirmation is necessary, for it is scarcely possible to conceive an experiment in which the difficulties of observation and the risks of subjective impressions would be greater.

Heidenhain's presentation of his argument from histology is so clear and persuasive, that it seems to have finally convinced many of his readers of the correctness of his scheme of renal activity. And the later work on the elimination of dyes has not received sufficient attention from physiological students. To summarize the discussion: it appears that all the ordinary stains are eliminated in the same general way, though some differences

in detail occur. The great mass of the dye passes through the capsule, sometimes in too dilute solution to stain it. In the tubules it becomes more concentrated through the withdrawal of fluid, and finally may be deposited in masses, this of course occurring more frequently under the less soluble dyes. Quite apart from this elimination of the dyes, the cells of the convoluted tubules and of the descending limb of Henle's loop show staining of the granules in their interior. This is a much slower process than the elimination of the dye through the capsule and differs in no wise from the granular staining observed in other cells, such as those of the nervous system; it has thus no bearing on the excretion of the pigments; it is unknown whether the dye deposited on the granules is derived from that circulating in the blood and lymph directly, or from that in the lumen of the tubules, but it may be presumed that the former is the source of the dye in the kidney cell as it is of that in the nerve cell.

A critical examination of the excretion of stains by the kidney thus fails to support Heidenhain's contention that they are secreted by the epithelium only. It is clear that while traces may escape by this path, the great mass comes from the capsule, and while these observations fail to lend any support to the view that the epithelium of the tubules is secretory in function, they establish that fluid eliminated by the capsule undergoes absorption in its passage through the tubules.

(*b*) *Excretion of Salts.*

An interesting experiment is described by Adami, who injected hæmoglobin intravenously into a dog, excised one kidney, then injected sodium nitrate, and when diuresis followed, removed the second kidney. Hæmoglobin was found in masses in the capsules of the first kidney, in comparatively few of the second. Adami infers that the rapid flow of urine had swept out the hæmoglobin from the capsule, and that this could only occur if the nitrate causes diuresis through action on the capsule. This promising method of investigation has not been pursued.

Biberfeld (1904, 1907) and Basler have attempted to follow the course of the excretion of ferrocyanide by the kidney; they injected sodium ferrocyanide intravenously, and when the salt appeared in the urine after a few minutes, they threw a solution of ferric chloride into the aorta to form

Berlin blue, and examined the kidney microscopically. Berlin blue was found in quantity in the interstitial tissues only, as appears very distinctly in Basler's figures; Biberfeld's statement that it occurs in the cells is not borne out by his figures, and similarly his view that the tubules are sometimes distended with the precipitate seems to rest on a mistake. The fact is that while the ferrocyanide is readily excreted by the kidney, the strongly acid, astringent ferric salts fail to penetrate through the cells in appreciable quantity. The Berlin blue is thus formed only in the lumen of the vessels and in the lymph spaces immediately surrounding them. No indication of the path of excretion of ferrocyanide is given by these experiments.

(*c*) *Uric Acid Excretion.*

The argument may be employed that the fate of the dyes in the kidney cannot give any information of value in regard to its normal activity, for these are not only exceptional visitants to it, but have in many instances a special relation to the cell contents different in character from such substances as constantly form constituents of the urine. It is therefore of importance to follow as far as possible the course of these normal constituents; unfortunately few of them give any reaction which can be used histologically, and urea, for example, has never been shown to be present in any one part of the kidney, though chemical estimations show it in larger amount than in any other organ. Uric acid and the urates are so insoluble that there seemed some hope of demonstrating their presence in substance, especially in the birds and reptiles, in which they form the great part of the renal secretion. Some of the older writers actually describe concretions of uric acid or urates in the cells of the so-called kidney of the snail (*Helix pomatia*), and also in the epithelium of the contorted tubules in the bird. But Bial (1890) pointed out that the concretions in the snail's kidney are really formed of guanin, which seems to reduce the low value of the old argument to zero; he found no trace of urate granules in the cells of the bird's or lizard's kidney, though they were present in the lumen. Even when urate or urea was fed to birds in quantity, they could not be found in the cells, and when the excretion was hindered by ligation of the ureter, no better success was obtained.

Heidenhain injected massive quantities of urate into the aorta close to the origin of the renal arteries and observed a large accumulation in the tubules but none in the interior of the cells, and Gurwitsch obtained the same results in frogs and was unable to

precipitate urate in the cells even by treatment with alcohol. An interesting observation was made by Nussbaum (1886), who states that in fish embryos urate is found in solid form in the Wolffian duct before the glomeruli are developed, but that after their appearance the urine becomes fluid and the urate masses disappear. Regaud and Policard state that in the lamprey and in snakes diverticula from the tubules are found lined with epithelium resembling that of the mammalian convoluted tubules, and with

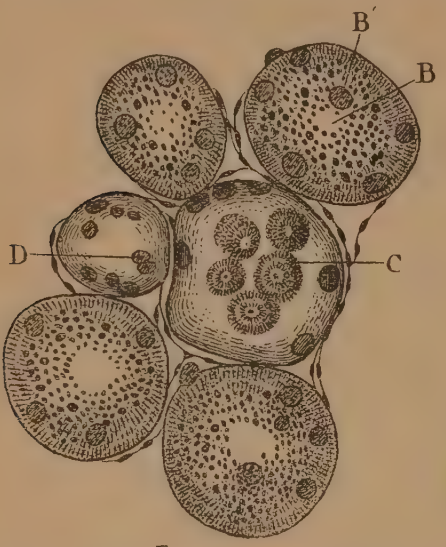

FIG. 12.

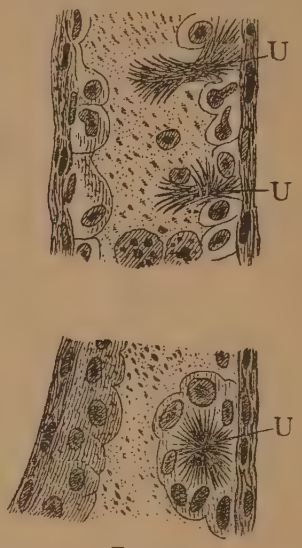

FIG. 13.

FIG. 12.—Excretion of uric acid in massive quantities. B, convoluted tubule containing numerous particles of uric acid in the lumen and extending into the cells. B′, a larger concretion of uric acid. D, narrow limb of Henle's loop containing larger aggregates of uric acid. C, collecting tubule with large spherical masses of crystals (chiefly after Minkowski).

FIG. 13.—Deposit of uric acid crystals (U) between and beneath the epithelial cells (after Minkowski).

the lumen filled with masses of secretion; they infer from this that the convoluted tubules are also secretory in function, but the argument is not convincing, for this organ in the lamprey is not the kidney of the mammal but a lower type, which may differ entirely in its functional activity from true renal epithelium.

Ebstein and Nicolaier, Sauer (1899), Minkowski (1898), and Eckert describe the histological appearance of the kidney under massive doses of uric acid in almost identical terms (Figs. 12 and 13). Minkowski fed dogs with adenin, from which uric acid is formed in the tissues, while the others injected uric acid dissolved

in piperazine subcutaneously or intravenously. The capsule and glomerulus were found to contain no uric acid, but quantities of urate were found all along the tubules.[1] Eckert states that these urate granules may be found in the rabbit's tubules five minutes after the injection of urate intravenously. In the cells of the convoluted tubules minute granules were observed by Sauer, while Minkowski figures large deposits either spherical or acicular, sometimes extending to the basal membrane, at other times apparently lying between or beneath the epithelial cells. According to Sauer, the character of the urate deposit varies in different parts of the tubule; in the convoluted portion, it is a mixture of fine and coarse granules closely packed on the surface of the epithelium; in the limbs of Henle's loop larger concretions make their appearance among the finer granules, and in the collecting tubules very large spherical masses of urate are seen. The epithelial cells are generally normal in appearance except for the presence of the urate masses in their interior, and the striated border is present though frequently torn and imperfect, perhaps from injury during the preparation of the sections. In some convoluted tubules the epithelial cells were torn loose and lay free in the lumen among the masses of urates; this may have arisen from the direct toxic action of the urate or, as Sauer suggests, may have been due to the tubules being blocked by the accumulation of urates lower down. The same appearance was presented by the kidneys in rabbits in which the cord was divided before the injection of urate; there was marked diuresis. When a part of the cortex was cauterized two days before the injection, the urates accumulated in the contorted tubules in the part below the scar, but were not found further down the tubules.

The presence of urate granules and masses in the epithelial cells led all of these investigators to the conclusion that uric acid is excreted by them. This may be correct, but the argument follows that which induced Heidenhain to ascribe the excretion of dyes to the same epithelial cells and the failure of this view suggests caution in accepting a new theory constructed on the same basis. The modern theory requires that urates like other constituents are furnished by the glomerulus in dilute solution and undergo concentration in the tubules until they may be

[1] Spiegelberg (1898) gives a similar account but does not enter into further detail.

stranded through the reabsorption of fluid. A certain amount of urate may be reabsorbed, for uric acid, according to the available analyses, is one of the "threshold bodies" and is not eliminated in proportion to the quantity present in the blood (p. 15). That a continuous concentration of the urate occurs in the passage through the tubules is shown by the increase in the size of the masses; the smallest granules are seen in the convoluted tubules, larger in the loop of Henle, and large spherical masses occupy the whole lumen in the collecting tubules. This evidence of the reabsorption of the fluid has been recognized by Suzuki, who believes that the urate is excreted by the convoluted tube in solution and is concentrated by the absorption of fluid in the lower tubules.

The occurrence of small granules of urate in the interior of the epithelial cells (Sauer, Eckert), or of large masses within and between the cells appears at first sight to be in opposition to the modern view and to suggest that the urate is on its way to excretion. But this accumulation of uric acid, like that of carmine in the inner border of the convoluted tubules, may arise from the poisonous action of large amounts of urate on those cells, for it is well known that such deposits are frequent is diseased tissue. Eckert injured the kidney in various ways—by ligaturing the ureter, anæmia, mercury, and phosphorus—and found that no urate concretions occurred, so that he concluded that the large deposits are not due to the cells being impaired. But in all of these lesions the capsule suffers as well as the tubules, that is, according to the modern view, the supply of urate to the tubules is diminished.

To many, however, the presence of these urate masses within and between the cells of the tubules seems to be indisputable proof that the urate is excreted by these cells. To such, a careful study of Minkowski's beautiful plate may be commended, for there may be found masses of urate lying not in the epithelium, but in the interstitial tissue between the tubules (see Figs. 10 and 11 in Minkowski's article). If the presence of urate in the epithelium indicates a secretory function, the masses in the interstitial tissue equally require the latter to be secretory; it should be added that these masses are described by the author as lying in the tubules, but in the figures given this is incorrect, as is shown by the relations of the tubules between which they lie.

It may be mentioned that the appearances presented by the

kidney in these experiments are not those of normal secretion, but that under massive and toxic doses of uric acid; and further that uric acid is normally present in very small quantities in the lower mammals, so that it may almost be regarded as a foreign body to some of them. During life it is probable that the urate is not present in the crystalline masses of the picture, but in solution, the crystals only forming as the kidney cools after excision.

Anten (1901) and Courmont and André (1905) have sought to demonstrate the presence of purine bodies in the renal cells in normal animals without the previous administration of urates. For this purpose they used either silver nitrate or silver chloride dissolved by the aid of ammonia solution. Anten injected the latter into the artery in living animals, while Courmont and André treated sections of the kidney with silver nitrate, which was precipitated by the urate, and then developed the section by the methods used in photography. They found minute granules in the interior of the cells of the mammalian tubes, while in the lower vertebrates these were contained in vacuoles; these deposits were not confined to the convoluted tubules, but also occurred in Henle's loop, but not in the glomerulus or collecting tubules. Unfortunately, these observations depend for their validity upon the assumption that the only substances in the cells which can react to silver chloride are the purines, and this is by no means to be regarded as established, for any diamino-acid present will precipitate silver in the same way as uric acid.

The excretion of uric acid by the kidney cannot be regarded as definitely establishing the secretory function of the tubules, as has been believed by some writers. On the other hand, it gives the same evidence of reabsorption in the tubules as is met with under the dyes.

(*d*) *Calcium, Phosphate, and Iron.*

Calcium is excreted by the kidney in considerable amount, and Roehl (1905) states that when lime salts are injected intravenously, they may be found in granules in the outer two-thirds of the cells of the convoluted tubules, and therefore concludes that the granules normally present in this position stand in close relation to the excretion of lime. When the kidney is injured by temporary ligature of the renal artery, or in poisoning with mercury, etc., deposits of lime are found in the epithelium and lumen of the tubules. Klotz states that this is preceded by cloudy swelling, necrosis, and fatty changes, and soaps may be detected by microscopic reactions. These soaps and fatty acids combine with the calcium of the lymph and form insoluble lime salts in which the fatty acids are slowly replaced by phosphoric and carbonic acids. Roehl regards this calcareous degeneration as dûe to the failure of the diseased cell to excrete the lime, which it is still capable of absorbing from the lymph, and which thus accumulates in its interior. How-

ever this may be, it bears no relation to the normal excretion of lime by the kidney, for calcareous degeneration occurs in other organs in which there can be no question of excretion.

Phosphate.—Sehrwald attempted to determine the distribution of the phosphate in sections of the kidney by the addition of uranium salts, and then of potassium ferrocyanide. The glomerulus and the inner layer of the epithelium was stained grey-white, while the rest of the organ was a diffuse blue. Sehrwald concludes that phosphate excretion, as shown by the grey-white coloration, occurs through the glomerulus. I have been unable to consult the original paper, but the interpretation seems inconclusive.

Another body which may be utilized to show the process of secretion in the kidney is *Iron*, which appears in the urine in traces after the salts are injected intravenously, though the great mass is slowly excreted by the epithelium of the large intestine. If sections of the kidney be treated with sulphide after the intravenous injection of iron, minute granules may be seen in the epithelial cells of the contorted tubules (Glaevecke (1883), Kobert (1883), Stender (1891)). Kobert and Stender also found iron in the capsule under some conditions, so that here, as in the case of organic stains, it is a matter of question whether the granules in the tubules are in process of secretion into the lumen or in course of absorption from it. Uranium apparently follows a similar course (Schneider, 1903) in the lamprey.

(*e*) *Chlorides, Sugar, and Urea.*

Some evidence as to the secretion of the kidney may be obtained by the quantitative estimation of the urinary constituents in the whole organ, and by the comparison of their concentration in the cortex and medulla.

Chlorides.—Langlois and Richet found about 0·3 per cent of chloride in the dog's blood and about 0·27 per cent in the kidney, or, if the animal had been bled, about 0·25 per cent. The urine contained a higher percentage, and the presence of some urine in the tubules gave the kidney a higher content of chloride than the other organs.

Lamy and Mayer (1905) state that the percentage of salts in the kidney remains constant even when chloride is injected into the blood previous to the excision of the organ.

Grünwald estimated the chloride of the cortex and medulla of the rabbit's kidney separately, and found that the medulla normally contains 2-3 times as much chloride as an equal weight of cortex. In rabbits fed on maize, and thus very much impoverished in chloride, the medulla was found to contain only 1·5-2 times as much chloride as the cortex, but during purine diuresis the proportion rose to 2·5 : 1. This merely indicates that the

urine in the tubules contained more chloride under diuresis than normally, however, and does not seem to prove that absorption occurs in the tubules normally, as Grünwald supposes; for most of the chloride obtained was in all probability in the interior of the tubules.

Sugar.—Lamy and Mayer (1905, p. 684) estimated the sugar of the kidney and found it vary directly with that of the blood, but the kidney always contained less sugar than an equal weight of blood, even when glucose had been injected intravenously and the urine contained a high percentage of sugar. They infer that the kidney does not accumulate sugar in its cells and then excrete it. This is confirmed by Levene who found 0·1-0·17 per cent sugar in the normal dog's kidney.

Nishi (263) compared the amount of sugar in the medulla and cortex in dogs, cats, and rabbits, killed by bleeding, and found that while the cortex contained 0·011-0·066 per cent of sugar, the medulla was either entirely free from sugar or contained only a trace. Even when the sugar of the blood was rendered abnormally high by adrenaline, no glucose was present in the medulla unless glycosuria was induced. He excludes the possibility of the sugar of the cortex being contained in the blood, and holds that it is present in the capsule and tubules in the cortex and disappears from the tubules of the medulla by being reabsorbed into the blood. There is no reason to question the correctness of Nishi's observations, and it is difficult to account for them except on his view that the sugar of the plasma filters through the capsule and is reabsorbed in the tubules under normal circumstances.

Traces of glycogen have been detected in the epithelium of the renal pelvis and collecting tubules of the rabbit, and also in the loop of Henle (Naunyn, p. 197), and v. Noorden has suggested that this glycogen arises from the reabsorbed sugar. Nishi could not detect glycogen in the normal rabbit's kidney by chemical methods of estimation, but found it in traces when hyperglycæmia was induced, and especially when this resulted in glycosuria.

Urea.—According to Heidenhain's experiments on the excretion of dyes and Sauer's on that of uric acid, the cells of the tubules continue to excrete when the flow of urine is arrested by section of the spinal cord. If urea is excreted by these cells, it must therefore accumulate in the tubules in the way that they describe for dyes and uric acid. Urea cannot be looked for by

histological methods, but such an accumulation could be recognized by the estimation of the total urea of the kidney. I have therefore estimated (91) the urea in the kidneys of a series of normal rabbits and compared it with that of a series in which the cord had been cut one or two hours previously; in these the urea had not escaped by the ureter, for there was no urine secreted, and the kidney should thus have contained in addition to the urea found in the normal animals that accumulated during the time the animal remained alive after the section of the cord. As a matter of fact, however, the kidneys of the operated animals always contained rather less urea than those of the normal ones.

In another series, one kidney was excised, the cord was then cut and the animal was kept alive for one to two hours, when the other kidney was excised, no urine having been passed in the interval. The first kidney (normal) always contained rather more urea than the second, so that there was no accumulation of urea after the flow of urine ceased. From these results, and similar ones obtained in the cat in the same way, it is clear that the excretion of urea ceases at the same time as the secretion of water by the kidney, and that the cells of the tubules are unable to accumulate it either in their interior or in the lumen in the absence of a flow of urine. This is opposed to the conception of Heidenhain, which he sought to establish through his experiments with dyes. It is possibly compatible with some theory of secretion, but not with that ordinarily held. On the other hand, the modern view requires urea, like the other constituents of the urine, to pass out by the capsule, and the cessation of the filtration owing to low blood pressure must lead to the arrest of the excretion of urea. This observation is thus in accord with the modern view, and has the advantage over those of Heidenhain and Sauer that the composition of the blood was not disturbed by the presence of a foreign dye or by the injection of any substance.

CHAPTER VI.

FURTHER DIRECT EVIDENCE AS TO THE FUNCTION OF THE TUBULES AND GLOMERULUS.

Frog's kidney—perfusion—destruction of tubules—injections into ureter—obstruction of ureter—synthetic activity and secretion—osmotic pressure in cells—gaseous metabolism—résumé of chapters v. and vi.

(*a*) *Experiments on the Frog's Kidney* (*Nussbaum's Experiment*).

An important method of investigation of the function of the glomerulus and tubules is afforded by the curious blood supply of the kidney in the frog. In this animal, as in the reptilia, the glomerulus is supplied by branches of the renal artery as in the mammal, and the efferent vessel breaks up into a second capillary system distributed over the tubules. But in addition, this capillary system receives a supply from the renal-portal vein, which has no analogy in the mammal; this vein collects part of the blood from the lower extremities, trunk, and genital organs, and carries it to the kidney, where it is distributed through the network on the tubules. The tubules thus are supplied from two sources—the efferent vessels from the glomeruli and the renal-portal vein; these both empty into a common capillary mesh-work, and there is thus complete anastomosis and complete mixture of the blood from the two sources; these capillaries can be injected either from the renal artery or from the renal-portal vein, and the tubules continue to receive a more or less adequate supply of blood if either the renal arteries or the renal-portal veins are ligatured, a fact which has often apparently failed to be appreciated. The blood from the capillaries of the tubules is finally collected in the renal veins which unite to form the inferior vena cava.

It is thus possible by ligaturing the renal arteries to cut off the blood supply of the glomerulus, while leaving the tubules

supplied from the renal-portal vein.[1] The first to use this method was Nussbaum. It requires some care, as the kidney is supplied by a number of small arteries, and all of these must be closed by ligature or cautery to exclude the glomerulus completely from the circulation. The success of the operation is shown by the injection of some dye into the aorta at the end of the experiment,

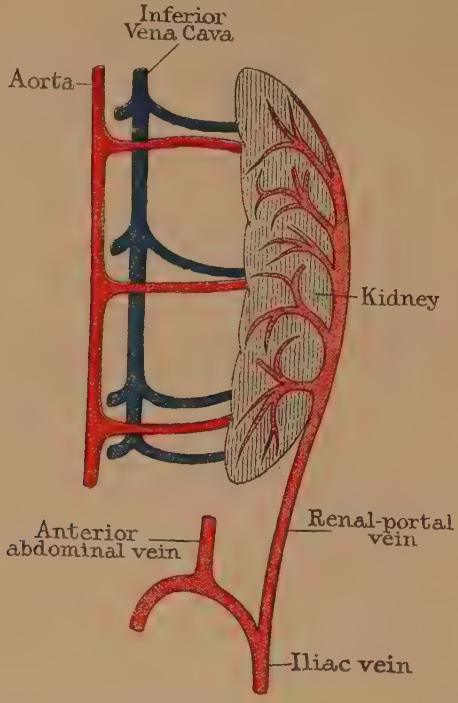

FIG. 14.—Diagram of blood supply of frog's kidney.

when none should be found in the glomeruli on microscopic examination; where this precaution has not been taken, the results cannot be regarded as conclusive.[2] The glomerulus cannot now be injected from the renal-portal vein (Beddard), since it is filled with a mass of clot and red blood cells. When the glomeruli

[1] Lindemann (1901) has attempted to adapt this method to mammals by injecting oil into the renal artery to block the glomerular vessels. It is obvious that this, if successful, would completely cut off the blood supply from both glomeruli and tubules, but as a matter of fact in his experiments the blood-flow was only reduced by about a half. No conclusions can be drawn from such experiments.

[2] The experiments of Adami (1885), Dreser (1885), and Halsey (1901) lose much of their value from the absence of this control.

are thus excluded from the circulation in the frog, the secretion of urine ceases, and the epithelium of the tubules undergoes rapid degeneration (Schmidt (1891), Beddard (1902)), and falls off in the course of two or three days ; this is apparently the result of a deficiency in the oxygen supply, for it does not happen when the animal is kept in an atmosphere of oxygen (Bainbridge and Beddard, 1906). No urine is secreted by these ligatured frogs if they are left undisturbed, but if urea is injected intravenously (Nuss-

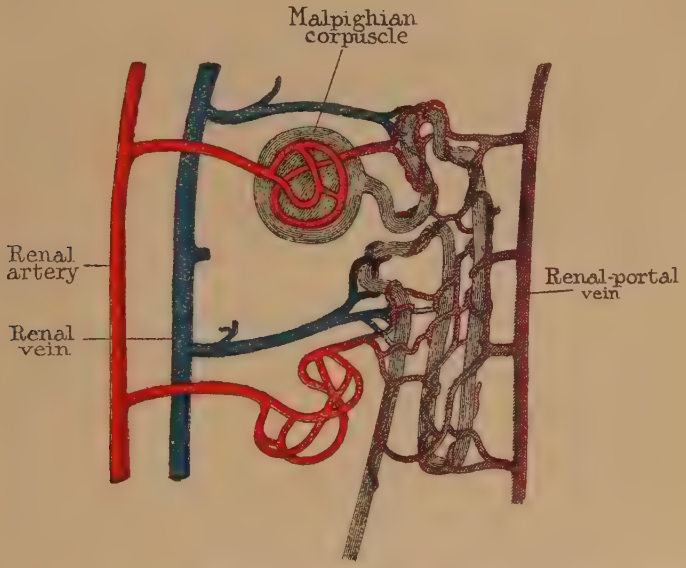

FIG. 15.—Diagram of blood supply of frog's kidney, showing capillary anastomosis between the efferent vessels from the glomerulus and the renal-portal system. One capsule and tubule is sketched in.

baum) or into a lymph-sac [1] (Bainbridge and Beddard), secretion follows, the urine amounting to about a quarter or less of that occurring in normal frogs from the same dose. This urine contains chloride, sulphates, and urea, and is distinctly acid. Dextrose injected in the same way causes no secretion (Nussbaum, Halsey), but when given along with urea the dextrose appears in

[1] Bainbridge and Beddard failed to obtain any secretion from urea unless the animal was kept in an atmosphere of oxygen, and therefore cast some doubt on Nussbaum's experiment; this appears to be unmerited, however, and the discrepancy in their results probably arises from Nussbaum's having injected the urea intravenously, while they threw it into a lymph-sac, from which it would reach the kidney more slowly and more dilute.

the urine (Bainbridge and Beddard). Sodium sulphindigotate injected intravenously appears in the lumen of the convoluted tubules without any secretion of urine occurring, while carmine, egg albumen, and peptone are not excreted [1] (Nussbaum).

This famous experiment of Nussbaum indicates that the secretion of urine is under normal circumstances dependent upon the glomerulus and capsule being intact. The secretion under urea is generally regarded as proving definitely that urea is normally secreted by the tubules, and as offering almost conclusive evidence in favour of Heidenhain's view of renal secretion; for he held that while fluid for the most part escapes by the capsule, the presence of an excess of urea or salts in the blood may induce a large flow from the epithelium of the tubules. Before this experiment can be regarded as of the importance which is often assigned it, further investigation is necessary. Thus it is desirable to be informed whether urea is the only substance causing secretion, or whether this property is shared by salts and other bodies; dextrose is apparently inert. Again, the relation of the urea secretion to the degeneration of the epithelium is still obscure, and it is not clear whether the fluid found in the bladder is a true secretion, or merely an exudation through the diseased epithelium aroused by some property of urea, which may have no bearing on its behaviour in the normal kidney; that the latter is the case might be argued from the presence of dextrose when it is injected along with urea, for dextrose does not seem capable of penetrating the cells alone. And certain discrepancies which appear between the results of Nussbaum's method and those of perfusion of the frog's kidney (see p. 79) need to be cleared up. Finally, it may be suggested that while the arterial circulation is eliminated from the glomerulus, that of the lymph is not excluded, and the importance of the lymph hearts in maintaining a circulation after that in the arteries and veins has been arrested, has recently been demonstrated in other organs.[2] In further investigations of this phenomenon, it would therefore be desirable to extirpate the lymph hearts.

I have no desire to belittle the importance of this experiment

[1] Schmidt states that if carmine and urea are injected together, the carmine appears in the urine and the tubules contain it in masses; but it may be questioned whether the glomerulus was completely eliminated in his experiments.

[2] See Abel and Macht (Journal of Pharmacology, 3, p. 581 (1912)).

in determining the theory of renal secretion, but the usual interpretation runs counter to the evidence regarding the excretion of urea and dyes in the mammals (see pp. 73 and 58). The final determination of the secretion of urea in the frog would of course weight the scales heavily in favour of a similar point of excretion in the mammal. But it must be recognized that the frog's kidney cannot be regarded as equivalent to the mammal's, for it still remains a mesonephros, a stage which the mammalian organ passes through in the course of its development, but which has evolved into a different organ in the adult.

The complement to Nussbaum's experiment has been carried out by Gurwitsch (1902), who tied the renal-portal vein and its branches on one side, and measured the amount of urine secreted by each kidney after the administration of urea. He found that passed by the kidney of the operated side considerably less than that of the normal one, and dyes injected appeared only in traces in the kidney with the occluded vein, while they were abundantly deposited in the tubules of the sound side. Gurwitsch explains the diminution of the urine on the ligatured side as due to the absence of the tubular secretion, and holds that his experiment demonstrates that the dyes are excreted by the epithelium and not by the glomerulus, and that it is therefore a final proof of the correctness of Heidenhain's contention and at the same time disposes of the suggestion that the tubules are absorbent in function. As a matter of fact, his results are inexplicable by either theory; for all are agreed that the capillaries of the tubules have a double blood supply—from the efferent vessels of the capsule and from the renal-portal vein. Occlusion of the latter does not therefore arrest the circulation in the capillaries, nor does it necessarily entail the stoppage of the activity of the tubular epithelium, as he supposes. Until Gurwitsch's results receive confirmation and further development, they remain incompatible with the known distribution of blood in the kidney. It is possible that they may have arisen from injury to the kidney in the course of the operation.

(*b*) *Perfusion of the Frog's Kidney—Cullis' Experiment.*

The perfusion of the frog's kidney, which was first done by Miss Cullis (1906), has since been practised by Bainbridge, Menzies, and Collins (1913, 1914), and by Rowntree and Geraghty (1912).

A cannula is tied in the aorta to supply the glomeruli, while another inserted into the anterior abdominal vein and pointing towards the feet carries fluid into the iliac veins and thence into the renal-portal system (see Fig. 14, p. 76). The urine is collected by a cannula inserted in the ureter, and the rate of perfusion may be measured by a fourth cannula in the inferior vena cava.

When oxygenated Ringer's fluid is perfused through the aorta at a pressure of 20-24 cm. of water, approximately the normal blood pressure of the frog, it passes through the glomerulus and then through the capillaries of the tubules, and finally escapes by the renal veins. The normal pressure in the renal-portal vein is about 10-12 cm. of water, and Ringer's solution perfused through it at this pressure passes through the whole capillary plexus on the tubules but does not as a rule reach the glomerulus. Under higher pressure (28-30 cm.) the fluid passes into the glomerulus and even into the renal artery and aorta (31).[1] It is of importance to remember that the tubules are supplied whether the kidney is perfused through the artery or the renal-portal vessel, and that this method only permits of the exclusion of the glomerulus.

When Ringer's solution is perfused through the artery, a considerable flow of urine follows, and the urine is of lower concentration than the Ringer's solution. When perfusion through the renal-portal is performed in addition to that through the artery, no increase in the urine follows, but it seems rather more dilute (32). When the vein alone is perfused at ordinary venous pressure, no urine is secreted, so that the urine formed from Ringer's solution appears to escape only by the capsule and not by the tubules. Deoxygenated Ringer's solution perfused through the artery is much less effective in causing secretion, and Cullis (1908) infers from this that the secretion through the capsule is a vital process. But this does not follow, for the permeability of the membrane may be reduced by lack of oxygen, and this would lead to a diminished filtration through it.

When urea (0·2-0·4 per cent) is added to the Ringer's solution perfused through the renal-portal vein, while the glomerulus is supplied with ordinary Ringer's solution, the urine is not more than when Ringer's solution is passed through both vessels; but when the urea solution is passed through the glomerulus, marked diuresis follows (Cullis). Thus urea, in much higher concentration than it can ever reach in the blood, appears to have no specific action on the tubules.[2] This seems to be

[1] The occurrence of this backward flow does not seem to have been appreciated by Cullis or by Rowntree and Geraghty, who usually employed a pressure of 25-40 cm. for both artery and vein; this invalidates some of their results.

[2] It is true that Cullis observed a slow secretion when this solution was perfused through the vein alone at high pressure, but here there was almost certainly a backward flow into the glomerulus.

opposed to the observation of Bainbridge and Beddard (p. 77), that in frogs with occluded glomeruli the injection of urea into a lymph-sac caused diuresis, for it is inconceivable that the blood could have contained 0·2-0·4 per cent of urea here. When stronger solutions (2-4 per cent) of urea are perfused through the vein at high pressure, a profuse flow of urine follows (Cullis, Rowntree and Geraghty). This is practically the same result as Nussbaum obtained with intravenous injection (p. 77), and it suggests that in each case some specific action of urea was in play—perhaps marked dilation of the vessels. It certainly cannot be regarded as throwing any light on the normal function of the kidney, and Barcroft (33) states that urea in this concentration perfused through the vein kills the cells, or at any rate reduces their metabolism to the vanishing point. It is obvious that the relation of urea to the tubules is still quite unknown. Lactose (0·5 per cent) perfused through the renal-portal vein at high pressure has the same effect in arousing secretion as urea (Rowntree, Fitz, and Geraghty, 1913).

Salts, such as chloride, sulphate, and nitrate of sodium, added to the solution perfused through the glomerulus, increase the flow from the ureter, and the exclusion of the venous circulation makes no change in this flow. Perfused through the renal-portal system, these salts cause no secretion of fluid, nor are there any adequate observations suggesting that they affect the tubules in any way.[1] Dextrose resembles these salts in its action. Cullis found it caused a slight flow of urine when it was perfused through the vein at high pressure, but this may have arisen from the glomeruli being involved.

Rowntree and Geraghty (1912) found that phenolsulphonphthalein added to the fluid perfused through the vein did not cause secretion, but when urea was added, the urine contained

[1] Cullis argues that the sulphate is excreted into the tubules on two grounds: (1) Because during diuresis from glomerular perfusion, when the arterial supply is suddenly cut off the secretion is not immediately arrested but falls off gradually; but this is probably explained by the fact that the glomerular filtrate is propelled along the tubules by means of the cilia, and the flow therefore continues until they have completely emptied the capsule. (2) Because when sulphate is perfused through the vein along with urea or caffeine, sulphate may be detected in the urine; but this merely indicates that caffeine and urea in causing secretion draw on the perfusing fluid and do not differentiate between the chloride and sulphate. Barcroft (33) found the oxygen consumption increase when sulphate was perfused through the renal-portal vein though no secretion attended it.

the pigment. Unfortunately they employed too high pressures, and the whole may have been due to filtration through the capsule. A number of other experiments performed by this method will be discussed in the chapters on caffeine and phlorhizin.

These perfusions of the frog's kidney indicate that the urine formed under the action of Ringer's solution, which approaches deproteinized plasma in composition, originates exclusively from the glomerular capsule, and that the diuresis arising from the presence of salts in excess is only possible when these salts reach the capsule. On the other hand, the tubules appear to have no power to secrete fluid under Ringer's solution alone, or reinforced by the diuretic salts. Urea in ordinary concentrations behaves like the salts, but very strong solutions perhaps cause a flow from the tubules. The results, as far as they go, favour the view that the whole of the constituents of the urine escape by the capsule, while very little light is thrown on the function of the tubules by this method.

The urine is not an unmodified filtrate, however, for its concentration is lower than that of the perfused fluid, and it is possible that the tubules may alter the composition of the filtrate by the reabsorption of some of the solid constituents. Bainbridge and his associates (1913) have attempted to determine this in a series of experiments in which they perfused a dilute solution of corrosive sublimate through the vein at low pressure while maintaining the arterial flow at a high pressure. The epithelium was destroyed by the poison, and they found the urine passed afterwards of the same concentration as the Ringer's solution; they infer that the unpoisoned tubule reabsorbs some chloride and thus reduces the concentration of the fluid passing over it from the glomerulus, but that this reabsorption ceases on the death of the epithelium, and the urine now consists of the unaltered glomerular fluid, which is isotonic with the Ringer's fluid. The weakness of this demonstration lies in the fact that when both glomerulus and tubule are poisoned with mercury and then Ringer's solution is perfused through the artery, a fluid exudes from the ureter, which is also isotonic with the Ringer; it may therefore be objected that in the experiments designed to kill the epithelium of the tubules, some of the poison reached the glomerulus and destroyed it also. It is true that all precautions were

taken to prevent this by keeping a high pressure in the artery, and that the glomerulus gave no reaction for mercury when examined histologically, but this objection cannot be altogether excluded. The same result was obtained when the tubule was poisoned with 0·1 per cent caffeine solution, while the glomerulus was perfused with Ringer's solution; the urine became isotonic, which the authors ascribe to the epithelium of the tubules no longer being capable of absorbing the chloride of the glomerular fluid. When the glomerulus was perfused with fluid devoid of oxygen, the urine was diminished in amount but was still hypotonic; here the Ringer's fluid continued to exude from the glomerulus, and absorption continued in the tubules, which were supplied with oxygen from the renal-portal vein. These experiments are in accordance with the modern theory and thus strengthen it; but they can scarcely be regarded as placing it on an unshakable foundation, as long as the immunity of the glomerulus to mercury and caffeine is not assured.

All these perfusion experiments suffer from certain defects which must be appreciated in order that the results may obtain their proper value. In the first place, the frog's kidney is a very small object, and there is no security that a fluid perfused through one part of it may not diffuse into other structures. Then, as Sollmann (352) has emphasized, there is danger in drawing inferences as to the behaviour of the mammalian kidney from observations made on the frog. And he further objects that a perfused kidney is constantly in a state of partial asphyxia and cannot be regarded as in any way capable of such activity as the normal organ. In perfusion of the mammalian kidney for example, and no one can speak with more authority here than Sollmann, the capacity of secreting urine is lost almost instantaneously after excision, though filtration still continues possible. Whether this is equally true for the cold-blooded animals may be questioned. But it is obvious that while the results of perfusion in the frog may lend support to the modern view of renal secretion, it cannot be said to have yielded any decisive arguments in its favour. On the other hand, far from supporting the view of vital secretion, it renews doubt as to the cogency of Nussbaum's experiment.

(*c*) *Ablation or Destruction of the Tubules.*

Many attempts have been made to determine the function of the renal tubules by observing the change in the secretion of the urine which follows when they are excised or put out of action by poisons. For this purpose Ribbert (1883) split open the kidney in the rabbit and gouged out the medulla, afterwards stitching up the cortex, which apparently healed successfully. The other kidney was excised. After this procedure he found the urine increased in amount and very dilute, containing approximately one-half or less of the normal amount of salts. His experiments are very insufficiently described, and he does not seem to have controlled the intake of food and water, as was necessary. Boyd attempted to confirm his results, but found that no increase in the urine occurred, while Hausmann on repeating Ribbert's extirpation under Meyer's directions, found that it was followed by an abundant flow of urine of low specific gravity and containing chloride and nitrogen in proportions approaching those of the deproteinized serum. Ribbert inferred from his observations that the tubules normally absorb part of the glomerular fluid, and that the removal of the tubules permits the glomerular fluid to reach the pelvis of the kidney unreduced in amount. This is also the explanation suggested for a marked increase in the urinary secretion which was observed in a patient in whom nearly the whole of the medulla of one kidney had been destroyed by an injury (Buyniewicz). But the force of this argument was broken by Bradford's (65) experiments on dogs, in which it was shown that the removal of a large part of the kidney substance comprising both cortex and medulla was frequently followed by a profuse secretion of dilute urine; in these the other kidney was removed, so that the total kidney substance left was reduced to about one-third of the normal. When still less remained, the urea increased also and rapid emaciation followed. And comparatively slight operations on the kidney are also followed by polyuria not infrequently. Thus removal of the external fibrous capsule often increases the urine to a marked extent (Ruschhaupt (321), Biberfeld (47), and Lindemann (220)). So that Ribbert's argument in favour of absorption by the tubules proves quite valueless.

The polyuria observed by Ribbert and Bradford where a large amount of kidney substance has been lost, has not been completely explained. Bainbridge and Beddard (1907) regard it as an incidental result of the operation, occurring comparatively seldom and perhaps arising from changes in the food and general nutrition. Pearce (1908) found that three-fourths of the total substance can be excised without any definite change in the nitrogenous metabolism, but when larger amounts are removed, disturbances of the gastro-intestinal tract lead to the changes characteristic of inanition. Pilcher (1913) was able to eliminate three-fourths of the kidney substance by ligature of the vessels supplying it, without inducing any significant change in the amount of urine or in its composition. The observations of these more recent investigators suggest that the polyuria noted by Ribbert and Bradford may have been only an indirect result of the renal lesion.

Others have tried to eliminate the activity of the tubules by means of poisons. The most notable of these attempts was made by Barcroft and Straub, who injected perchloride of mercury or large quantities of caffeine through the renal circulation by a special method which permitted the resumption of the blood circulation subsequently. The kidney was gravely injured, as was shown by the low oxygen consumption and also by the fact that the injection of sodium sulphate intravenously was followed by comparatively slight diuresis; the urine also differed from that in ordinary sulphate diuresis in containing practically the same content of chloride and urea as the blood plasma. The authors appear to accept tacitly that the glomerular filtration is unaffected by the passage of mercury perchloride in the strength of 1 in 400 through the renal vessels, and that the tubules alone suffer from its action; they hold that their experiments establish the secretory activity of the tubules, but they do not clearly indicate what the tubules normally secrete. Their observations may be more consistently explained on the assumption that the corrosive sublimate destroyed to a large extent both the glomerular capsule and the epithelium of the tubules, and that the fluid which escaped from the ureter was of the same nature as that which may be collected when a dead kidney is artificially perfused. In the one experiment in which they injected caffeine as a poison in the cat, sulphate injection subsequently caused comparatively little secretion, while chloride was followed by a fair amount of urine; possibly the kidney had recovered partially in the interval, possibly the chloride injection was larger in amount.

In any case these experiments do not appear to establish the secretory function of the tubules, nor can they be regarded as either supporting or negativing the view that absorption occurs here. I have discussed them only as examples of a type of experiment, which is made on the assumption that the heavy metals destroy the epithelium of the tubules more readily than the glomerular capsule. It is quite true (see chapter on Nephritis) that histologically more evidence of degeneration is offered by the tubules, but this is accounted for by the fact that the epithelium here is much more readily examined than that of the capsule. And a cell may be killed by a poison without any visible change being appreciable if it is examined by ordinary histological methods of hardening.

Botazzi, Onorato, and De Bonis injected a solution of sodium fluoride into the ureter upwards in order to destroy the epithelium of the tubules. They state that the urine from the kidney thus injured is less in amount and lower in concentration than that from the normal kidney of the opposite side. The objection to this method is that the tubules cannot be injected from the ureter in the living animal (see p. 87). Sodium fluoride thus applied can only corrode the pelvis of the kidney.

None of these methods of eliminating the action of the tubules are successful, and none of them give any indication as to the function of the epithelium.

(*d*) *Injections into the Ureters.*

A number of investigators have attempted to solve the question of reabsorption in the tubules by injecting fluids into the ureters under pressure and examining the kidney histologically afterwards or seeking for the fluid injected in the other organs or secretions.

An experiment of a different nature was performed by Ribbert (1894), who injected a dilute solution of carmine directly into the medulla by means of a fine needle, and then found the tubules of the medulla and some convoluted tubules filled with granules ; if the injection really entered the tubules directly, this would prove the absorption of fluid, leaving a concentrated solution and granules of carmine, but it may be contended that the injection reached the interstitial tissue and that the carmine was excreted into the tubules in concentrated form or in granules. The experiment certainly cannot be regarded as satisfactory evidence of absorption.

A. Huber (1896) forced a solution of potassium iodide into the dog's ureter towards the kidney at a pressure of 35-42 mm. Hg., and found iodide in the saliva after some minutes; he argues that this proves absorption from the tubules. Ferrocyanide and sugar injected in the same way may be found in the urine from the other kidney (Basler); and Tuffier (1894) states that strychnine injected into the pelvis of the kidney gives rise to poisoning. These experiments show that absorption occurs, but this may be from the pelvis of the kidney, not from the tubules, and the arguments of Huber against this view do not appear to be convincing. Basler, injecting indigo solution into the rabbit's ureter, found crystals in the collecting tubules and perhaps higher, but none in the epithelium. Henderson (1905), using the same method, found indigo-carmine in the lumen of the loop of Henle and convoluted tubules, and also in the interior of the cells lining them. And the urine from the opposite kidney contained indigo. But in his successful experiments, a pressure of 90 mm. of mercury was employed, and this is stated by Lindemann (1904-5) to be sufficient to rupture the walls of the tubules. Henderson could not find any such lesion, but the possibility of its occurrence cannot be dismissed. Lindemann injected Berlin blue and solutions of dyes in oil into the ureter, and found none in the kidney except in some of the straight tubules; and he considers that his results negative the view that absorption occurs in the tubules; but this is far from being the case.

None of these experiments can be regarded as showing in any way that absorption occurs in the tubules, but on the other hand, none of them can be used as an argument against it. For, in the first place, none of the experiments were done with absorbable substances; it is true that Basler injected glucose, but in 4-12 per cent solution, which is not taken up by the tubules. If absorption is to be investigated, sodium chloride or bromide or dilute glucose should be injected. In the second place, the experiments of Lindemann show distinctly that the tubules cannot be injected from the ureter in the living animal with any degree of certainty. This agrees with some observations of my own, in which a column of dilute salt solution stained with carmine was attached to the ureter so that the outflow could be measured; only enough fluid escaped to fill the pelvis and ureter, and no further movement occurred for an hour or more. And even when the renal cortex was pared away with a scalpel, no fluid issued from the cut tubules, showing that the solution had not entered them; the column remained unchanged in height until the whole of the cortex was pared off, and generally until the pelvis was actually cut into. The explanation appears to be that pressure in the pelvis flattens down the papilla and thus closes the orifice of the tubules. The lips of the orifices thus form a sort of valve,

which allows the escape of fluid from the interior of the tubule provided it can overcome the pressure in the pelvis, but prevents regurgitation from the pelvis to the tubule. A rise of pressure in the pelvis may thus retard the escape of fluid from the tubules, as will be discussed in the next subsection. In these experiments, therefore, unabsorbable fluids were used, and they did not reach the epithelium of the tubules, so that no conclusions can be drawn from their results.

(*e*) *Complete or Partial Closure of the Ureter.*

The urine secreted by one kidney after the closure, complete or partial, of its ureter has been compared with that secreted by the normal one of the opposite side in a number of researches. The underlying assumption is that normally each kidney secretes urine in practically the same amount and of the same composition, and that any differences observed in these experiments may be attributed to the resistance opposed to its outflow. This assumption is not entirely correct, however, for in normal animals and in man the urine of the two kidneys is not always identical in amount or composition, as has been shown through the use of ureteral catheters by Kapsammer, Albarran, Barringer, and others; the differences are especially marked if the urine is collected for only short periods; the longer the periods the more are the inequalities obliterated. And in animals under sufficient anæsthesia, the urine on the two sides is often practically identical in amount and composition over long experiments. The inequalities seen in observations in man without anæsthesia are often due to reflex changes in the renal vessels (p. 12).

In many of these experiments one ureter was completely ligatured for several hours, and the urine contained in it was then compared with that secreted by the other kidney in the meantime. Thus Hermann (1859) found in the dog that the removal of the ligature was followed by a rapid flow of urine containing a lower percentage of chloride and urea than that of the normal urine of the other side, but with a higher total of each. Pfaundler, repeating this experiment, ligatured the ureter for two to five hours, and found on releasing it that more urine flowed from it than had been secreted by the opposite kidney during the whole time, and that it contained a lower percentage

of chloride, urea, and total solids (as measured by the freezing-point). There is great difficulty in interpreting these observations, for it is not clear whether the urine flowing from the reopened ureter is that which has been secreted during the period of obstruction only, or whether it is a mixture of the stagnant urine with that secreted rapidly after the ligature is removed; it seems impossible that the 28 c.c. of urine in Pfaundler's experiments could have been contained in the ureter and kidney. And Hermann and Guyon mention a rapid secretion after the ureter is released; this rapid secretion from pressure in the ureter has been mentioned already (p. 12) as in all probability of reflex origin. But if, as I suggest, the urine examined by these authors was really such a mixture, its comparison with the normal urine has no point; in order to make any useful comparison, the whole kidney should have been removed before the ligature was loosened; the urine then obtained from the ureter might correspond more or less as regards time relations with that obtained from the opposite side during the period of ligation.[1]

Others have partially obstructed one ureter and compared the urine secreted against pressure with that of the normal unobstructed side. Hermann (1862) found both the amount of urine and the urea decreased on the obstructed side. Lepine and his pupils (1888 and 1913) and Lindemann (1897) in more exact series of experiments found the urine and chloride fall in nearly equal measure, while the urea was only slightly reduced;[2] the percentage of chloride thus remained practically the same on the two sides or was lower on the obstructed side, while that of the urea rose considerably here. An example of Lepine and Porteret's results may be given:—

In an anæsthetized dog a cannula was placed in each ureter; on the one side a resistance of 40 cm. of water was opposed to the flow, while the other ureter was free. Five per cent sodium chloride was injected intravenously to cause diuresis; the experiment lasted two hours, and the urine from each side was measured and analysed separately.

[1] Guyon and Rosow found that after prolonged ligature of the ureter, the pressure in its interior falls, and finally, after some weeks, the secretion ceases and the kidney undergoes atrophy. Suzuki has made a careful histological examination of such kidneys after varying periods of closure of the ureter, and finds that carmine continues to be excreted in traces for many weeks. If, as he holds, the carmine passes into the tubules in solution, this indicates that practically the whole of the water in which it is dissolved undergoes reabsorption.

[2] In Lindemann's first experiment there is an arithmetical error, which leads to an erroneous statement.

	Urine.	Urea.		Chloride.	
	In c.c.	Total.	Per cent.	Total.	Per cent.
From free ureter .	73	0·146	0·2	0·35	0·48
From obstructed ureter	11	0·121	1·1	0·044	0·40

Indigocarmine injected intravenously behaved in the same way as urea, appearing in smaller total amount but in higher percentage on the obstructed side. Lindemann shows that the pressure in the ureter employed in these experiments was insufficent to interfere with the circulation in the kidney, though a pressure of 50 mm. of mercury in the ureter impairs the venous outflow.

In a paper in 1902, I was able to confirm and extend the results of these authors by showing that sulphate and phosphate resemble urea in their behaviour in similar experiments on the rabbit. More recently, Allard has examined the question in a case of *ectopia vesicæ* in man, in which he was able to obstruct one ureter partially and to compare the urine of this side with that of the unobstructed ureter; water, urea, and sodium chloride were given by the mouth and the urine of each ureter was analysed for urea and chloride. His results are in complete accordance with those previously published; on the obstructed side less water, urea, and chloride were secreted, but the deficit in water and chloride was much greater than that of the urea. An example may be given.

A litre of dilute tea was given fifty minutes before the observations began. The resistance was 40-60 cm. urine or about 30-45 mm. Hg.

Time, mins.	Unobstructed Ureter.					Obstructed Ureter.				
	Urine.	N per cent.	N total.	NaCl per cent.	NaCl total.	Urine.	N per cent.	N total.	NaCl per cent.	NaCl total.
1-30	263	0·079	0·206	0·0585	0·154	164	0·122	0·2	0·0526	0·0863
40-70	251	0·087	0·218	0·0468	0·117	64	0·135	0·0864	0·041	0·0262
Total	514	0·082	0·424	0·0528	0·271	228	0·125	0·286	0·0494	0·1125

Thus the obstruction lessened the water and chloride more than one-half, while the urea was only one-third less and its percentage thus rose from 0·08 to 0·12.

Gogitidse in his experiments on dogs injected with urea or sodium chloride intravenously in very large quantities, found the urine and chloride lessened on the obstructed side in almost equal proportions, while the urea was rather less diminished; but he appears to have analysed the urine collected for too long intervals to admit of accurate observation of the progress of secretion.

A different result was obtained by Steyrer in observations made on patients with partial occlusion of one ureter; in these the urine on the obstructed side was greater in quantity than on the normal one, while the total amount of urea and chloride was lower. This divergent result may perhaps indicate that the prolonged obstruction in these cases had led to some secondary changes in the kidney.

Another divergent result was obtained by Schwarz (1902) and by Brodie and Cullis, who found that on placing a resistance in one ureter the urine on that side actually increased in amount. This is almost unquestionably due to a reflex from the ureter, which has been mentioned already (p. 12), and the conclusions reached by these authors will receive discussion under sulphate diuresis.

The interest in these experiments lies in the fact that they show that the water and chloride differ in their relation to the kidney from the urea, sulphate, phosphate, and indigocarmine; for there is practical unanimity that when the flow is lessened the water and chloride fall greatly in amount, while the other constituents undergo much less reduction.

While the facts are almost generally accepted, much divergence is met in interpreting them. The best account of the view of Heidenhain's followers is given by Allard, who holds that the pressure in the ureter is transmitted along the tubules to the glomerular capsule, and results in lessened activity of the secretory cells, and thus in a slower secretion of water and chloride; the secretion of urea in the tubules is impaired partly by direct pressure on the cells, partly by the diminished flow of glomerular fluid, but the epithelium of the tubules does not suffer to the same extent as the capsule, and the urea is therefore not so much reduced under obstruction as the glomerular secretion. The objection to this view is that it takes no account of the proportions of the pressures involved. If the glomerular capsule separates water and chloride from the urea, sugar, and colloids of the blood, it must work against an osmotic resistance of about 400 mm. of mercury in doing so. Is it reasonable to suppose

that an additional burden of 15-20 mm. through ureteral obstruction is capable of reducing the product of the activity from 80 to 90 per cent? The case is still more difficult when the lessened excretion of urea is considered. For even if the urine contains only 1 per cent of urea, this means that the secretory epithelium must overcome a pressure of 2800 mm. Hg in passing it from the blood to the tubules; in the experiment given the percentage is much lower, so that the cells must have had a large reserve of force, yet an additional load of only 30-40 mm. is supposed to have been sufficient to reduce their output by about 30 per cent.

The modern view holds that the pressure in the ureter is propagated along the tubules to the capsule and thus opposes the filtration pressure; so far it agrees with Allard, but while the energy of secretion which is required by his view is very high, the filtration pressure of the modern view is comparatively low, and it is thus more readily conceivable that a low resistance in the ureter may reduce the amount of filtrate considerably. The percentage composition of the filtrate is the same as that on the free side, but the total amounts of urea and chloride are, of course, smaller. The smaller amount of filtrate passes more slowly along the tubules, and more time is allowed for the reabsorption of the absorbable contents, water and sodium chloride, and these accordingly reach the ureter in smaller amount, while the urea, which is not absorbed, reaches it in unchanged quantity; the percentage of urea thus rises, not because urea is added to the filtrate by secretion in the tubules, but because the water is taken up by them.

It is important to recognize that the increased absorption is not due to the increased pressure in the tubules, but to the diminished filtration from the action in the capsule. The absorption in the tubules is normally opposed by an osmotic resistance of several atmospheres owing to the presence of unabsorbable contents in the filtrate, and the counter-pressure of some 20-30 mm. through ureteral obstruction cannot be of any significance.

This view, which I brought forward in 1902, is considered by Allard, but is rejected by him on the following grounds: the diuresis was caused by water, and the object was to get rid of the excess of water with as little loss of other constituents, such as sodium chloride, as possible; now if obstruction allows

of a more complete recovery of the useful constituents of the filtrate, it might be expected that more sodium chloride would be reabsorbed, while the water would remain and escape in the ureter. As a matter of fact, however, the percentage of chloride is almost the same on the two sides, and it may be calculated that the fluid absorbed from the filtrate contained slightly less chloride on the obstructed side. The argument appears to proceed on the assumption that the chloride of the urine in this experiment was lost to the tissues through failure of the absorption, which ought to have been obviated by the improved absorption on the obstructed side. But it is to be remarked that even on the free side the conservation of the valuable sodium chloride was very successful, for over 500 c.c. of water was eliminated at a cost of only 0·271 NaCl, which is hardly more than would have been excreted in the same time had there been no diuresis. And it may be questioned whether the salt which was collected from the obstructed ureter and was estimated as sodium chloride by Allard, was really a sodium salt at all; for Macallum and Benson have shown that the dilute urine from drinking large amounts of water contains potassium in larger amounts than sodium. The chloride of the urine estimated by Allard in this experiment was therefore not the sodium chloride, which it is to the advantage of the organism to retain, but for the most part (perhaps entirely on the obstructed side) was potassium chloride, which it is desirable to eliminate, and which is probably absorbed by the tubules (see potassium) only to a limited extent. When Allard caused diuresis by sodium chloride, he found that on the obstructed side a larger proportion of chloride than of water was absorbed; here the filtrate contained a larger proportion of the absorbable sodium chloride and a smaller of the potassium salt. The tubules were thus able to remove more of the total chloride.

The results of experiments with partially obstructed ureter are more uniform than those of many other methods of investigation of the renal activity, and the marked effects of a slight degree of resistance in the ureter are difficult to understand on Heidenhain's theory, which demands the activity of comparatively large secretory forces. On the other hand, they are compatible with the view of filtration at low pressure and subsequent reabsorption in the tubules.

(*f*) *Relation of Synthetic Activity to Secretion in the Kidney.*

A curious argument is used by Asher and Tropp in favour of the vital secretion of chloride. They induced a moderate degree of diuresis in dogs by the injection of sodium chloride, and then on throwing a mixture of glycin and benzoic acid into the blood stream, found that the urine contained a higher percentage of chloride without any increase in the amount of fluid. They argue that the formation of hippuric acid from glycin and benzoic acid is due to specific activity of the cells of the tubules, and that this is accompanied by increased elimination of chloride, and they infer that chloride excretion is due to specific activity of the renal cells. This argument seems to have impressed some later writers, though it scarcely appears convincing, especially if it is borne in mind that when glycin and benzoic acid are injected without chloride, no such increase in the chloride of the urine is observed. The truth is that the conditions are too complicated to allow of any definite conclusion. The percentage of chloride in the urine during salt infusion is apt to vary from many cases, such as slight variations in the rate of infusion; and the effects of glycin and of benzoate injections are unknown. If one pours together half a dozen solutions taken at random from a chemical laboratory, no chemist can tell offhand what the resulting mixture may contain, and the condition of affairs is far more complex when a series of reagents is poured into the blood stream. It is quite possible that glycin or benzoates may drive the chlorides of the tissues into the blood in the same way as urea or nitrate, and that this may account for the increased chloride of the urine. At any rate such experiments cannot be regarded as offering support to either view of renal activity unless the exact constitution of the plasma is first investigated.

(*g*) *The Osmotic Properties of Kidney Cells.*

The fluid obtained by mincing the kidney was found to have a higher concentration than the blood (Sabbatani), and this is of course to be expected, since the fluid contains some urine along with the intracellular fluid, lymph, and blood. The molecular concentrations of the cortex and of the medulla have been compared by finding the strength of salt solution from which each is capable of taking up water. By this method Filehne and Biberfeld (1902) found the molecular concentration of the cortex equivalent to 1·5-1·8 per cent salt solution, while that of the medulla was higher. Hirokawa made a more detailed examination of this phenomenon, and found that in all animals the cortex is isotonic with a solution of 1-2 per cent of sodium chloride, and that this is not altered by changes in the concentration of the urine. The concentration in the medulla varies in different species, but is almost always greater than that of the cortex. The more concentrated the urine, the higher is the concentration

of salt necessary to keep discs of the medulla unchanged in size. If the urine is very dilute, on the other hand, the osmotic pressure of the medulla may be as low as that of the cortex. Hirokawa therefore concludes that the osmotic pressure in the discs is not that of the renal cells, but that of the urine contained in the tubules of which the discs are composed. And thus the urine in the tubules of the medulla is more concentrated than that in the cortex. This change in concentration may arise either from secretion of solids by the tubules or by absorption of fluid from them; but he holds that as the medulla consists mainly of the loop of Henle, which is not supposed to be secretory in function, the process must consist in the absorption of fluid. This, of course, is not indisputable, for the discs of medulla must have contained the thicker portion of Henle's loop, which many hold to be secretory in nature, and also the collecting tubules. Hirokawa then holds that in the cortex the urine becomes about 1½-2 times as concentrated as the plasma, while in the medulla it may rise to as much as 9 times the concentration of the plasma.

Siebeck and Ehrenberg have recently investigated the osmotic processes and the imbibition occurring in the frog's kidney or in small pieces of the mammalian kidney. Their results do not seem to bear directly on the problems of the living kidney, and the subject is not ripe for discussion at the present time.

(*h*) *The Gaseous Metabolism of the Kidney.*

Barcroft and Straub compared the consumption of oxygen by the kidney during normal secretion with that in diuresis from the injection of Ringer's solution and hypotonic, or hypertonic solutions of sodium chloride. They found practically no change in the oxygen consumption, although the amount of urine was increased nearly twenty-fold (see Fig. 8, p. 36). The analysis of the urine during the diuresis from Ringer's solution is compared with that of the normal secretion and that from sulphate in the following table :—

	Normal.	1st Na_2SO_4 Diuresis.	Ringer Diuresis.	2nd Sulphate Diuresis.
Chloride calculated as NaCl, per cent	0·42	0·22	0·86	0·39
Sulphate calculated as Na_2SO_4, per cent	0·26	1·25	0·38	2·0
Urea	4·4	0·28	0·15	0·25
Oxygen used per gr. kidney per minute	0·4 c.c.	0·9 c.c.	0·3—0·4 c.c.	0·9 c.c.

A large increase in the fluid, chloride, and sulphate excreted by the kidney occurred during the infusion of the Ringer's solution, yet the activity of the kidney, as measured by the oxygen consumption, was unchanged. This is quite unintelligible on the view that each of these constituents is passed through the kidney epithelium by the vital activity of the cells, and there is every reason to regard this observation as supporting the view that the diuresis was due to filtration, the pressure for which was supplied by some force external to the kidney, that is, by the heart contractions. In only one feature did the normal urine suggest greater elaboration than that passed under Ringer diuresis—the greater concentration of urea; for while the actual amount of urea eliminated under the diuresis may probably have been larger per minute than in the normal condition, it was much more concentrated in the latter. This may suggest that the chief activity of the kidney consists not in the actual transmission of molecules and ions through the cells but in the concentration of certain constituents, of which urea may be taken as the type. And this is supported by the observations on sulphate diuresis. For under sulphate, as opposed to chloride, diuresis the oxygen consumption shows a marked increase. This is not apparently due to the excretion of sulphate in itself, for during the Ringer diuresis in this experiment a much larger amount of sulphate was eliminated per minute than in the normal secretion, yet no increase of oxygen consumption occurred. The rise in the oxygen consumption in sulphate diuresis may thus be attributed to the work done in separating the sulphate from the water of the plasma. This would be in entire agreement with the modern theory that the actual passage of the constituents of the urine occurs by filtration, a purely physical process, while the concentration of such constituents as the sulphate or urea takes place through vital absorption in the epithelium of the tubules. When an unabsorbable salt, such as sulphate, is present in quantity in the filtrate, more work than usual has to be performed in overcoming the osmotic resistance, and a larger oxygen consumption may therefore be anticipated.

These observations on the consumption of oxygen by the kidney in diuresis thus appear to be diametrically opposed to the view that the urinary constituents are secreted by vital activity, while they support the view that the process is partly a

filtration, and are reconcilable with the modern theory that the elaboration of the urine is performed by reabsorption through vital cellular activity. In justice to the authors it must be added that they limit their interpretation to the statement that the Ringer diuresis "is the result of a physical process which does not entail any increased output of energy on the part of the tubules".

Barcroft (33) has attempted to extend this method to experiments on the perfused frog's kidney after the method described on p. 79. The results are very puzzling; the oxygen consumption is increased in the frog perfused through the renal-portal system only, when caffeine is added to the Ringer and causes diuresis, but the same increase is seen on the addition of sulphate, which causes no diuresis. When Ringer's solution has been perfused through the renal-portal vein only, and perfusion is begun through the artery also, there is a marked rise in the oxygen consumption, even though the total fluid passing through the kidney is unchanged. Barcroft considers this increase too great to be accounted for by the activity of the capsule alone, and suggests that the passage of the fluid along the tubules arouses their epithelium to greater activity; this would be in accord with reabsorption occurring in the tubules. But the method of perfusion is open to some criticism (see pp. 80, 83). Barcroft's experiments were few in number, and the results so far obtained do not admit of any conclusions except hypothetical ones. The similar effects of caffeine and sulphate on the O_2 consumption, along with their dissimilarity as far as any visible renal activity is concerned, seem to require further examination before much weight can be laid on the arguments drawn from this method.

Résumé of Chapters V and VI.

An unbiassed examination of the direct evidence for specific secretion in the kidney must lead to the confession that the results of so much labour are disappointing and unconvincing. As far as the capsule is concerned, neither Heidenhain nor any of his followers has ever succeeded in bringing a tittle of direct proof that the cells are actively engaged in the process, and the experiments of Barcroft and Straub (p. 95) show that a great increase in the urine can occur without change in the work of the kidney, which points directly to filtration rather than active secretion.

In the tubules, the histological observations of the excretion of dyes and uric acid, which were formerly regarded as definite proofs of active secretion, have lost much of their value for this purpose under more critical examination. There may possibly

be some active excretion of the dyes and of uric acid, but this is far from being established in either case.

The excretion of urea (p. 73) does not conform to the views advanced by Heidenhain and apparently accepted by most subsequent upholders of vital secretion in the kidney. A certain support is lent to this view by a superficial reading of the Nussbaum experiment (p. 75), in which urea is shown to cause a flow of urine in the frog. But when the results of Cullis' perfusion are taken into account, this action of urea is seen not to be so simple and not to offer so valuable evidence in favour of special secretion as has generally been supposed.

As regards absorption in the tubules, it is curious enough that the examination of the elimination of dyes and uric acid should give much more definite evidence of the absorption of fluid than of the excretion of these bodies. And Nishi's observations on the distribution of sugar in the kidney are difficult to explain otherwise. Similarly, the results of experiments with partial obstruction of the ureter are readily explained on the absorption view, while they are unintelligible on the theory of special secretion. The other methods of investigation which have been described in the last two chapters either require further development before their results can be accepted, or are not adapted to give definite evidence, and therefore need not be discussed in this summary. In short, examination of the various methods by which direct evidence, of the functions of the glomerulus and tubules has been sought, supports the modern view of filtration in the capsule and reabsorption in the tubules rather than that of special vital secretion in each of these.

In the further chapters little direct evidence will be available for either theory, and the reader is invited rather to weigh how far the results can be brought into accord with known physical principles, and how far they require the assumption of unknown vital forces. The facts given in the last two chapters justify an unbiassed examination, for the direct evidence for vital secretion is certainly not formidable, and is at least equalled by that for the modern view. If the latter proves able to bring the further observations into accord, it is unnecessary to resort to the complications of special secretion and special stimulation.

CHAPTER VII.

BLOOD SUPPLY AND KIDNEY SECRETION—THE MECHANICAL FACTOR.

Circulation and secretion—puncture diuresis—minimal efficient circulation—venous obstruction—general consideration—secretion pressure—transfusion and plethora—defibrination.

THE relations between the circulation and the activity of the kidney was the theme of the earliest experimental investigation of urine formation. Goll, a pupil of Ludwig, showed in 1854 that in the dog the fall in arterial pressure following from stimulation of the vagus or bleeding is accompanied by a diminution of the flow of urine along the ureters; on reinjecting the blood the secretion is restored, though not to its original rate. On raising the pressure in the aorta by tying off a number of its branches, the secretion of urine increases appreciably. The changes in the urinary secretion are not directly proportional to those in the blood pressure, but always moves in the same direction. One of these early experiments of Goll may be cited for its historical interest.

	Urine in 30 mins.	Solids, per cent.	Average Blood Pressure.
Normal	61·23 47·50	2·7 2·1	139·3
During bleeding . . .	2·06	?	57·0
After reinjection of blood . .	19·34	4·5	121·0

In these experiments of Goll's the kidney was only one of many organs involved, and the changes in the secretion might have been the indirect results of changes in other organs. Hermann (1862) therefore reduced the pressure in the kidney vessels alone by compressing the renal artery of one side by means of a screw clamp. As soon as the calibre of the artery was materially

reduced by the clamp, the amount of urine fell, to rise again to the normal as the vessel was released. Complete closure of the artery arrested the secretion forthwith.

The same change in the secretion may be effected through the nerves controlling the circulation. Thus Ustimowitsch (1870) showed that section of the renal nerves is followed by an increased secretion of urine, and this has been frequently confirmed by others. Division of the splanchnic nerve on one side similarly increases the secretion of the corresponding kidney in the dog, as was shown by Bernard in 1859, and has been confirmed by many (104, 198, 195).[1] Stimulation of the splanchnic lessens the urine or arrests it altogether. In the rabbit, section of a splanchnic nerve is generally followed by the cessation of the secretion in both kidneys, because the arterial pressure falls much more from this operation than in the dog, in which it may be reduced by only 30 per cent. Burton-Opitz and Lucas (1908) measured the outflow from the renal veins in the dog by means of their "stromuhr," and found that stimulation of the renal nerves or of the splanchnic lessened the outflow from the kidney through vaso-constriction, while division of the renal nerves or of the splanchnic was followed by an increased blood-flow indicating vaso-dilation (see also p. 8).

Division of the cord in the cervical region or destruction of the vaso-constrictor area in the medulla oblongata arrests the secretion in both dogs and rabbits (Bernard, Eckhard, 1870), and reduces the blood pressure to a very low point. In the cat, however, I find that complete section of the cord is not necessarily followed by anuria, as the blood pressure is less reduced in these animals, and it is often necessary to destroy the cord by pithing to stop the secretion of urine entirely. On the other hand, stimulation of the medulla oblongata electrically, or by asphyxia (Grützner, 1875), or anæmia may arrest the secretion of urine, and the kidney becomes ischæmic, as is shown by its colour and by the fact that less blood escapes from a wounded surface (Grützner). But if the renal nerves are divided previously, stimulation of the medulla causes diuresis and no ischæmia of the kidney (Lamy and Mayer, 1903).

When a marked fall in the general blood pressure is induced

[1] Schwarz (1899) denies this, and holds that section of the splanchnic lessens the secretion, but stands alone here.

by large doses of chloral given intravenously, the urine may be lessened in amount or stopped completely, even when it has previously been profuse from saline injections (Loeb, 1906, and others). But a moderate amount of chloral may increase the secretion, if it is diminished by marked medullary activity.

In short, a rise of the general blood pressure always increases the flow of urine, unless when it is accompanied by vaso-constriction in the kidney, while a fall of the general blood pressure lessens the secretion, unless the kidney vessels are dilated beyond those of the rest of the body.

It has been a question whether the increased flow of urine is to be ascribed to the rise in the blood pressure increasing the filtration mechanically (Ludwig), or to its accelerating the flow through the capillaries and thus improving the nutrition of the secreting cells (Heidenhain). In all the instances cited above, in which the urine increases along with a rise in arterial pressure, there is also renal vaso-dilation and acceleration of the flow through the kidneys, while in the instances in which the general blood pressure rises but no augmentation of the urine follows, the blood supply of the kidney is reduced by vaso-constriction. The determining factor is not the general blood pressure, but the capillary pressure in the glomerulus, and an increase in this leads to acceleration of the flow through the kidney except under one condition, namely, obstruction of the renal vein, and here special conditions arise which will receive attention later (p. 104).

Sollmann (1905, p. 280) has examined the mechanical factors in the dead kidney perfused with saline, and finds that when the pressure of the perfusion fluid is raised, the fluid exuding from the ureter increases, while on reducing the pressure, the exudate is reduced. Here only physical forces can act, and it is suggestive that in the kidney simple filtration may simulate the reactions seen in the living organ. Richards and Plant, who believe that they have succeeded in maintaining the kidney alive by artificial perfusion, state that the amount of urine secreted depends on the rate of flow rather than on the pressure in the artery.

It may be taken as common to all views of renal secretion that the larger the blood supply to the kidney, the greater the secretion. Ludwig did not fully appreciate this factor, but it is an essential feature of the modern view (see p. 106).

The characters of the urine in the diuresis caused by section

of the renal nerves have not been exhaustively studied. Frey (1907, p. 154) states that during the diuresis after section of the renal nerves the concentration of the urine (*A*) remains higher than that of the blood. Knoll found that after section of a splanchnic in the dog the specific gravity of the urine and the percentage of solids and of urea are reduced, but the total quantities are increased, while Grek states that the chloride is increased both absolutely and in per cent. The meaning of these changes, which are common to many forms of diuresis, will receive attention later.

Puncture Diuresis.

Soon after his observation that puncture of the floor of the fourth ventricle is followed by glycosuria, Claude Bernard found that a similar puncture rather higher in the ventricle causes a marked increase in the urine, which remains free from sugar. This was confirmed by Eckhard (1869-72) in a series of important papers. In these early experiments the puncture polyuria appears to have been irregular in appearance, and the urine often contained some sugar and albumen, but more recent investigators seem to have overcome these difficulties, and a simple diuresis may generally be obtained. The funiculus teres is the point aimed at in the medulla oblongata. Irritation of the lower part of the vermiform process of the cerebellum is also stated by Eckhard to be followed by polyuria in the rabbit, and Bechterew found that stimulation of the sigmoid gyrus (*G. precruciatus*) of the cerebrum accelerates the flow of urine from the kidney of the opposite side. The polyuria from puncture of the funiculus teres has been examined with some attention by a number of recent writers, more especially in its relation to the polyuria which is known clinically as diabetes insipidus. A puncture on one side generally increases the urine from both kidneys (Jungmann and Meyer), though Eckhard found it less on the injured side than on the other one.

The diuresis is often preceded by a phase in which the urine is diminished or completely arrested (Eckhard); this probably arises from a short fall in the general blood pressure observed by Jungmann and Meyer, who state that the polyuria only sets in when the blood pressure recovers. The urine then flows rapidly, and this increased secretion lasts from twenty-four to forty-

eight hours (Jungmann and Meyer), after which the normal secretion returns. Kahler states that if instead of simple puncture a corrosive is applied, the polyuria may remain for weeks, but this is disputed by Finkelnburg. The diuresis is attended by an increase in the total chloride of the urine and often in the percentage, especially when the animal has been fed on a diet poor in chloride previously (Jungmann and Meyer). The nitrogen of the urine may be increased or decreased in total but is always in lower percentage. The blood becomes more concentrated, as shown by a rise in the percentage of protein. These are the constant accompaniments of diuresis in the rabbit, and do not indicate any specific action on the kidney such as Jungmann and Meyer postulate.

This polyuria is of the same nature as that induced by division of the splanchnic nerve or of the renal fibres. It is true that Eckhard opposes to this some experiments in which puncture caused polyuria after division of the splanchnic and most of the renal nerves, but Jungmann and Meyer could not confirm these. The discrepancy may perhaps be explained by varying effects on the blood pressure, which has to be controlled in these experiments. For it is obvious that puncture may fail to cause diuresis if the preliminary operation has reduced the blood pressure very considerably. The evidence points to the puncture causing impulses to be emitted from the medulla oblongata, which pass through the splanchnics and reach the kidney through the renal nerves. As to the nature of these impulses, Eckhard concluded on insufficient grounds that they were secretory, and Jungmann and Meyer consider that the increase in the chloride points in the same direction; but the chloride is almost invariably increased during diuresis in the rabbit, and their argument is therefore of no value. The puncture polyuria appears to arise from action on the vasomotor centres controlling the kidney which is either of the nature of vaso-dilator stimulation or of vaso-constrictor depression, or very possibly comprises both of these.

After Claude Bernard's diabetes puncture in rabbits, the urine increases in amount, and contains a larger amount of chloride as well as sugar; the presence of sugar is due to nervous action on the liver, which leads to hyperglycæmia, and which may be excluded by the previous section of the hepatic fibres (Eckhard, 1872), or of the left splanchnic (Jungmann, 1914). On the other hand, division of the renal nerves alone prevents the characteristic poly-

uria, while leaving the glycosuria (Jungmann). In the polyuria puncture, therefore, the fibres controlling the kidney alone are affected, while the "diabetes puncture" entails injury both of these and of those governing the glycogen function of the liver. Both sets of fibres run in the splanchnic nerves, those to the liver apparently only on the left side.

Minimal Blood Pressure Compatible with Secretion.

Ustimowitsch found that the secretion of urine ceased when the blood pressure fell below 40 mm. of mercury in the dog, and this is also true for the cat in my experience. In the rabbit, v. Schroeder found urine secreted at 40-50 mg. -Hg under caffeine, and these values agree with the experience of most later writers. Grützner observed secretion continue until the pressure reached 30 mm. of mercury. The lowest arterial pressure at which urine is secreted under normal composition of the blood, may thus be taken at 30-40 mm. mercury.

I have observed in the cat that the amount of blood passing through the kidney, when the pressure has been reduced until the secretion ceases, is about one-third of that under normal pressure.

When the blood is diluted by the intravenous injection of urea or salts, the kidney may continue to secrete though the blood pressure is far below the point at which it would cease with normal composition of the blood (Ustimowitsch, Grützner). Thus Gottlieb and Magnus (140) observed secretion in the rabbit under saline infusion with a blood pressure of 30 mm., and even of 13-16 mm. On the other hand, if the renal vessels are constricted by stimulation of the medulla oblongata, these saline injections may fail to cause any diuresis, even at a high general arterial pressure (Grützner). (See Chap. VIII.)

Constriction or Closure of the Renal Vein.

When the outflow of blood from the kidney is hindered by narrowing or closure of the renal vein, the pressure in the glomerular capillaries must rise until in complete closure it almost reaches that in the renal artery. Here then there is an increase in pressure without an increase in flow through the capillaries, and it seemed possible that a decision might be reached of the old question which of these is the essential factor in mechanical

diuresis (see p. 101). Goll found that obstruction of the renal vein causes no increase in the urinary flow, but on the contrary rapidly arrests the secretion completely.[1] Paneth made a very careful examination of the effects of partial obstruction of the vein, and agrees with his numerous predecessors that the urine is lessened in amount and soon contains albumen and blood if the outflow is retarded for long; the secretion returns to the normal if the compression lasts only a short time. When the secretion is deficient through compression of the vein, an intravenous injection of sodium nitrate causes marked diuresis, even when the arterial blood pressure is kept unchanged by the simultaneous injection of chloral; thus saline diuresis is not prevented by the passive congestion arising from venous constriction. De Souza (1901) confirms the observations of Goll and Paneth. Rowntree, Fitz, and Geraghty (314) succeeded in maintaining partial constriction of the vein on one side in the dog for periods of some weeks, and found that the urine was sometimes increased slightly. On prolonged slight constriction, the urine contains albumen, casts, and blood without any significant change in the amount of fluid, but as the constriction and passive congestion are increased, the secretion diminishes, while the albumen, blood, and casts increase, and the excretion of such foreign substances as lactose, iodides, and dyes is much delayed.

The diminution and arrest of the secretion from pressure on the renal vein was explained by Ludwig (1861) by the suggestion that the swollen veins press upon the tubules in the medulla and narrow or close them so that no urine can reach the ureter; he supported this by experiments in which the excised kidney was perfused and the fluid escaping from the ureter was diminished by constriction of the renal vein. Contrary results were obtained by Kobert, who at Tammann's suggestion (1896) perfused excised kidneys with various protein-free solutions, and found that the fluid from the ureter increased when the outflow from the vein was arrested by ligature. But Sollmann (1905), in a careful series of experiments, failed to confirm Kobert's observation, finding

[1] This has been confirmed so often that Schwarz's statement (1899) that closure of the vein increases the secretion for more than half an hour, must be based on some error in technique, probably the preliminary defibrination of the animal (see p. 118). His further view that ordinary ligature of the vein is followed by clotting and that the anuria arises from this, has been controverted by De Souza and is unquestionably erroneous.

with Ludwig that pressure on the vein in the perfused kidney never increases the fluid from the ureter, but always leads to a diminution. And as Sollmann's experiments were more numerous than Kobert's,[1] and are given in detail, there seems every reason to accept Ludwig's statement that in the diminution and arrest of the secretion when the vein is obstructed, the mechanical pressure on the tubules is an important factor; Sollmann suggests that in addition the glomerulus may be distended so as to fill Bowman's capsule almost entirely and thus to reduce the filtering surface.

In addition to this mechanical obstruction to the flow along the tubules, another factor may intervene; for while the pressure in the capillaries of the glomerulus rises, the blood current through them is slacker, and the capsule may suffer from asphyxia, to which it responds rapidly. Again, as Tammann first suggested, the escape of fluid through the capsule must lead to a concentration of the remaining constituents of the blood and to an increase in the osmotic resistance which they offer to the secretion of fluid. This increased resistance must rapidly lead to a failure of the capsular fluid, whether the passage be regarded as a simple filtration or as an active secretion. Paneth's observation that salines continue to act in partial obstruction of the vein, appeared to him to be in opposition to Ludwig's view that the lessened secretion is due to mechanical obstruction of the tubules. This does not seem a necessary consequence, for it may be supposed that the pressure of the fluid in the tubules in saline diuresis is increased and thus overcomes the resistance. And whether this is true or not, the effects of the intravenous injection of saline will be shown to arise mainly from the dilution of the colloids of the plasma, so that Tammann's factor in the reduced secretion under venous compression comes less into play, and there is thus a larger secretion than before the injection.

General Considerations of the Mechanical Factor in Secretion.

The kidney differs from other secretory glands in its close relation to the general circulation. No other gland is known to respond so readily to changes in the blood pressure, and none of

[1] Metzner suggests that the discrepancy between the results of Kobert and Sollmann may arise from the former having used ox kidneys for perfusion, the latter dog's; but this does not appear very plausible.

them ceases to secrete like the kidney when the pressure reaches a definite low level, though the circulation persists. Heidenhain objects to this anuria under low pressure being regarded as due to the low tension in the vessels, and suggests that the real cause is the diminished blood-flow through the kidney. The increased secretion, which Ludwig and his pupils ascribed to high pressure, he similarly considers to be due to the increased rate of circulation in the kidney, which provides a richer oxygen supply and thus augments the activity of the cells, and at the same time supplies them with larger amounts of material to be excreted. But however that may be, the fact remains that the secretion of the kidney differs widely from that of other glands in its dependence on the circulation. This was emphasized by Brettel (1869), who compared the effect of changes in the circulation on the parotid gland of the sheep with that on the kidney; each gland he found to secrete approximately the same amount of fluid, but the parotid secretion was practically unaffected by the measures which Goll had shown so effective in the renal secretion (vagus stimulation, bleeding, etc.). The Bowman-Heidenhain view then gives no explanation of this close relationship of secretion and circulation, but it is in no way incompatible with it, the specific secretory activity of the kidney merely differing in this respect from that of the more typical glands of the body.

On the other hand, the effect of changes in the arterial pressure is completely explained by the filtration theory. For filtration through the capsule can occur only if the pressure on the vascular side is higher than that on the opposite side of the membrane, and the greater the pressure in the vessels the more rapid the filtration. If the whole of the plasma passed through the capsule, filtration would doubtless go on at a very low pressure, the only resistance being the actual friction in passing through the membrane. But the colloids are retained, and the arterial pressure must thus be sufficient to overcome their osmotic resistance. Starling (1899) pointed out in a brilliant piece of work that the osmotic resistance of the proteins of serum may be taken as about 30 mm. of mercury, while most observers had found the lowest limit of blood pressure compatible with renal secretion to be about 30-40 mm. He considers that the glomerular filtration continues as long as the pressure in the capillaries is sufficient to overcome the osmotic resistance of the colloids; that is, the pas-

sage of fluid through the glomerular capsule corresponds to the passage through any dead membrane which holds back the proteins, and does not offer evidence of any vital activity whatever.

It has been objected to this that the carotid pressure, which is that usually measured, cannot be regarded as equivalent to that in the glomerular capillaries, which must be much lower owing to the resistance met in passing through the narrow afferent vessels. The pressure in the glomerulus has been held to be about 20 per cent below that in the carotid artery; this estimate is little more than a guess based on observation in other organs, and it may be remarked that the anatomical relations of the renal arteries and their branches are apparently adapted to give a higher pressure head in the capillaries than that prevailing in most other organs, and that the very rapid blood-flow through the kidney supports this. But adopting this deduction of 20 per cent, we find the minimal pressure at which secretion continues, to be 30-24 mm. of mercury in the capillaries, while the osmotic resistance of the colloids has been variously estimated as 20-34 mm. Considering the difficulties attending the determination of each of them, the coincidence of these values is remarkable.

Secretion can continue only as long as the colloids of the plasma are not notably increased in concentration; for their osmotic pressure then rises and the capillary pressure is no longer able to overcome it. Thus if any stagnation occurs in the glomerular capillaries, the increasing osmotic resistance of the colloids, as the fluid filters off, arrests the further filtration. The modern view thus requires not only an adequate pressure in the capillaries but also a rapid circulation through them. The bearing of this free blood-flow is illustrated by a tracing given by De Souza and reproduced in Fig. 16. The urine was measured as it flowed from one ureter, and the rate of blood-flow was altered by alternately raising and lowering a tube connected to the corresponding renal vein by means of a cannula. The outflow is seen to vary with the pressure in the vein, and the secretion of urine follows the curve of the venous flow, though it falls slowly throughout the experiment owing to a gradual fall of the general blood pressure from loss of blood. In this experiment the mechanical obstruction of the tubules described by Ludwig can scarcely have occurred, for the pressure in the vein is never much above the ordinary venous pressure, the changes occurring from a very moderate positive to a distinctly negative pressure. Unfortunately De Souza used animals whose blood had been de-

fibrinated, and this appears to act deleteriously on the kidney (see p. 118).

This reduced blood supply to the glomerulus may also play a part in other instances in which the urine is reduced from changes in the circulation. Thus a fall in the general blood pressure, or ischæmia of the kidney through constriction of its

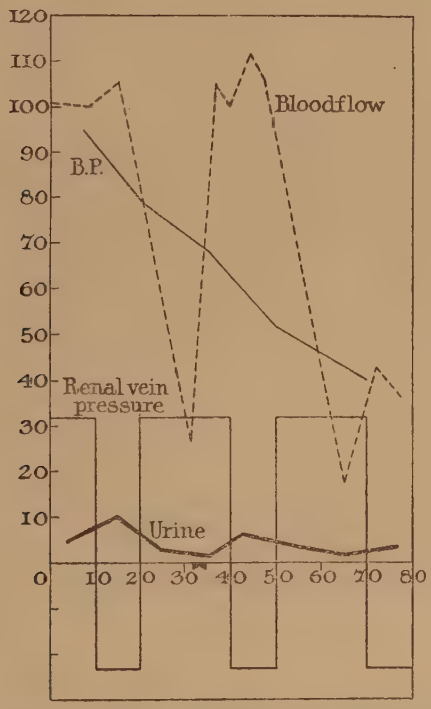

FIG. 16.—The influence of changes in the pressure in the renal vein on the blood-flow through the kidney (- - - -) and the secretion of the urine (——) (De Souza).

vessels, may not only reduce the pressure available for filtration, but may also limit the amount of fluid available without undue increase in the colloid concentration. The old dispute, whether the pressure or the velocity of the blood-flow is the important factor, is thus settled by the recognition that both are essential.

Pressure of Secretion.

The pressure of the urine in the pelvis of the kidney is negligible in ordinary conditions, but when a manometer is tied into

the upper part of the ureter and obstructs the flow, the mercury soon begins to rise, and, after a period which varies with the rat of secretion, attains a maximum at which it stands for ten to fourteen hours (Obniski); after this it sinks gradually from exhaustion of the animal. The maximum pressure varies in different animals and under different conditions. On an average it may be taken as about 50-70 mm. of mercury in the dog (170, 159, 148, 216, 177, 140). Higher values have been observed in some animals; thus Starling (1899) found a pressure of 70-95 mm. in one dog, and Obniski states that he obtained pressures of 105-110 mm., and in one case of 130 mm. during very profuse diuresis from salines and urea. Very low pressures are frequently observed.

A certain relation obtains between the blood pressure and the secretion pressure, as was early noted, the pressure in the ureter tending to rise and fall with that in the arteries, though the parallelism is not complete. Under ordinary conditions, the maximum secretion pressure is found to lie about 40-60 mm. below that in the aorta, but this is subject to many exceptions, which may probably arise from the factors discussed by Henderson (164). Here again the kidney departs from the typical secretory gland. For example, the pressure in the submaxillary duct is found to exceed that in the arteries, and to be largely independent of the blood pressure as long as an adequate supply of blood reaches the gland. And again, the theory of special secretion affords no explanation of this aberration from the usual type in the kidney, which it describes as acting by the same mechanism.

On the other hand, these observations have always been regarded as supporting the view of glomerular filtration. For this can proceed only as long as the pressure on one side of the filter membrane is higher than on the other. If the outflow is obstructed, the filtration ceases as soon as the pressure is equal on the two sides. In glomerular filtration the capillary pressure is the driving force, and if this is taken as 20 per cent lower than the carotid pressure, the difference between the pressure in the capillaries and the maximum ureter pressure, that is, the difference of pressure on the two sides of the capsule, amounts to about 30-50 mm. of mercury. The pressure requisite to force

the filtrate through the capsule against the osmotic resistance of the plasma colloids is about 30 mm. of mercury, and the capillary pressure must therefore always exceed that within the capsule by this amount. The correspondence between these figures is close enough to be regarded as strongly supporting the filtration view, as was pointed out by Starling (1899). An even closer approximation would doubtless be attainable if the capillary pressure could be measured directly instead of being calculated from that in the carotid artery. It may be objected that a certain amount of force should be credited to the work of driving the urine along the tubules, and that no provision is made for this in the scheme. But as the pressure in the ureter rises and the current along the tubules slackens, this work diminishes until, when the maximum pressure is reached, the movement ceases and no energy is consumed therefore.

An important objection to this view was brought by Heidenhain (1883, p. 327) and has been repeated by Brodie (1914). They state that according to the filtration-reabsorption view a large amount of absorption occurs in the tubules, and the maximum pressure in the ureter must therefore measure not the filtration pressure, but "the pressure which just suffices to effect complete absorption of all the glomerular filtrate"; for the resistance to the outflow raises the pressure in the tubules, and this, they suppose, promotes the absorption, so that they find it difficult to understand how the high ureter pressure is compatible with the theory. This objection appears to me to arise from a misconception of the view to which it is opposed. For the modern view is that the dilute glomerular fluid undergoes absorption of water and some solids in its passage along the tubules, and thus becomes a concentrated solution of solids which are taken up with difficulty by the epithelium. When a resistance is opposed to its escape by the ureter, the flow becomes slower, the absorption of water and permeating solids is more complete, while the concentration of the unabsorbable constituents rises and, through their osmotic pressure, more and more resistance is offered to the absorption of water. Finally, the tubules become filled with a fluid to which both the ordinary exits are barred, that by the ureter by the manometer, and that by absorption through the epithelium by the fact that the cells cannot overcome the osmotic

resistance of the solids, by which they are impermeable. The column of fluid in the tubules then transmits the pressure existing in the capsule to the manometer.

A comparison may serve to elucidate the problem: a manometer in the carotid artery gives no indication of the intraventricular pressure, because the blood escapes into the arterioles of the body; but if the latter are constricted, the manometer approaches the ventricular pressure, and will finally indicate it when the arterioles are completely closed; the carotid represents the ureter, the main blood-flow the passage of the filtrate through the absorbing epithelium, the constriction of the arterioles the growing failure of the epithelium to cope with the increasing resistance to absorption as the osmotic pressure rises.

It may be necessary to repeat here what has already been discussed (p. 92), that the mechanical obstruction of the ureter promotes absorption only by retarding the flow and thus affording the epithelial cells more time for their activity. The actual pressure exerted by the fluid in the tubules can have no significant effect, for the absorbing power in the epithelial cells must be measured in metres of mercury, and the addition of some 50-70 mm. pressure can matter little.

In ordinary conditions then, the maximal ureteral pressure is reached when the osmotic resistance of the fluid in the tubules balances the absorbing force. But when a very rapid diuresis occurs, the tubules may be unable to absorb the gush of filtrate rapidly enough, even though the osmotic resistance is low; the manometer pressure thus rises rapidly, and may fall slightly when the diuresis falls off and more time is allowed for reabsorption. And this fall may occur while the blood pressure rises, as Gottlieb and Magnus observed; thus in an experiment under caffeine, the ureter pressure during diuresis was 66 mm., the blood pressure 105, while later the ureter pressure was 52, and the blood pressure 110. This fall in the ureter pressure must be explained through reabsorption of fluid from the tubules, as they admit. If the excessive filtration continues, the maximum ureter pressure may be maintained, not because the tubules are filled with fluid in itself unabsorbable but because it is too abundant for the cells to cope with it.

The maximal ureter pressure is not in the long run affected

by the rate of filtration. It is generally attained more quickly during abundant secretion (Henderson), for the reason discussed in the last paragraph. But the final value seems to be practically the same whether the flow of urine is rapid or slow (Brodie). And this of course is in accord with the modern view; for the pressure goes on rising until the absorbing force of the epithelium is neutralized, either by the osmotic pressure of the contents of the tubules or by their overwhelming amount, and the manometer then represents the pressure in the capsule. This pressure is the difference between that in the glomerular capillaries and that necessary to drive the filtrate through the capsule. Changes in the latter factor, such as occur in diuresis, might be expected to be registered by the ureter manometer, but they are indistinguishable from changes in the capillary pressure by our present methods. The observation that when the normal ureteral pressure is high, diuresis has little further effect on it, while when it is low, it rises on diuresis (Gottlieb and Magnus), may perhaps bear on this.

The speed with which the maximum ureter pressure is attained, is determined by the rate of the flow from the capsule and the osmotic resistance offered by the solids of the urine. It would be of interest to compare the speed of movement of the mercury under moderate diuresis from substances differing in the rate of permeation through the tubules, e.g. sodium chloride and urea. Under chloride diuresis, Gottlieb and Magnus found a very large difference between arterial and ureter pressure, and this may perhaps be due to the ready absorption of the chloride.

The ureter manometer follows rapid changes in the capillary blood pressure (Henderson, Fig. 17), such as occur on stimulation of the vagus, because the fall of blood pressure allows the glomerulus to retract and the fluid in the tubules escapes into the empty capsule. The same effect follows without change in the blood pressure from stimulation of the renal nerves, or, with a rise of blood pressure, from that of the splanchnic. In each case the glomerulus is retracted, and room is made for the fluid from the tubules. On the other hand, the available space in the capsule is limited, and it may thus happen that under a marked fall in arterial pressure the ureter manometer shows less change. The manometer now indicates not the filtration pressure after the change in blood pressure, but a higher one; and such errors

can only be avoided by frequently emptying the ureter and beginning from zero again. Neglect of this precaution led Gottlieb and Magnus to assert that the pressure in the ureter may actually exceed that in the arteries.

FIG. 17.—Kidney Volume by Oncometer (O.); Blood Pressure (B.P.), and maximal Ureter Pressure (U.P.) of the dog during stimulation of the Vagus (V) and the Splanchnic (S) (V. E. Henderson). The ureter pressure follows the arterial during vagus stimulation, but moves in the opposite direction during the vaso-constriction from excitation of the splanchnic.

The Effects of Transfusion on the Secretion of Urine—Plethora.

The effects of blood-transfusion on the kidney have been examined repeatedly, and it is agreed that the amount of blood in the circulation may be increased by 50-100 per cent in this way without any increase in the urine (285, 240). Care must be taken, however, that the animal from which the blood is drawn is in the same general state of nutrition as that into which it is injected, and that no diuretic substance has been given it recently. Thus Magnus (240) found that when the bled animal had received an injection of sodium sulphate previously, its blood caused some increase in the urine, and even when the blood of a fasting animal

was injected into another fed one, this was followed by a slight transient diuresis; curiously enough, the reverse does not hold true to the same extent, the injection of blood from a fed animal into a fasting one being much less effective (Asher and Waldstein). The results seem to be the same whether the transfusion is a direct one from artery to vein, or the blood is defibrinated and injected (Ponfick).

During transfusion the pressure in both arteries and veins rises very considerably in the animal which receives the blood, and the kidney is found to be much increased in volume (Magnus); as there is no diuresis, this can only mean that the renal vessels are dilated. The conditions therefore seem to be those which

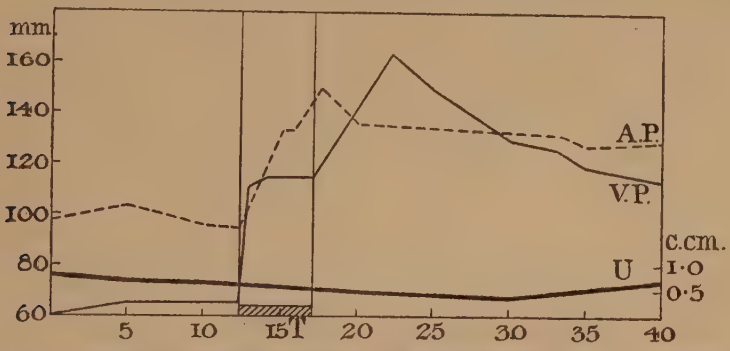

FIG. 18.—Graphs of the arterial pressure (A.P.), venous pressure (V.P.), and secretion of urine after the transfusion of blood (T.). (After Magnus.)

Heidenhain regarded as favouring the secretory activity of the renal cells, and at first sight they would seem also to be those in which filtration through the capsule must increase, for the rise in the pressure in the renal artery and vein must increase that in the capillaries of the glomerulus, and thus give a greater head of pressure for filtration through the capsule. The excess volume of blood in the vessels is not relieved through the kidneys, however, but by exudation into other organs. Magnus showed that this elimination of plasma occurs very rapidly after transfusion; for example, in three to four minutes after the transfusion the vessels had got rid of about 40 per cent of the total volume injected and in twenty minutes of about 56 per cent. If the plasma of the transfused blood be taken at two-thirds of its total volume, it will be seen that in three to four minutes nearly two-thirds of the injected plasma is lost from the vessels into the tissues, leaving

about one-third of the plasma and all the corpuscles. But the plasma in all probability does not escape from the vessels unchanged; as in the normal lymph formation, a fluid probably exudes which is much poorer in proteins than the plasma. Three or four minutes after transfusion then, the blood is burdened with a large bulk of corpuscles floating in a plasma which has increased to some extent in volume and to a much greater extent in content of proteins. The blood pressure is high, partly no doubt from the increased total mass of the blood, partly, it may be surmised, from the difficulty with which it can be driven through the vessels owing to the abnormal richness in corpuscles. But this rise in the blood pressure, which in itself would favour diuresis, is counteracted by the increased osmotic resistance of the proteins of the concentrated plasma. The absence of diuresis from transfusion of blood is therefore in complete accord with the filtration theory.

The transient diuresis which occurs after the transfusion of blood from a fasting animal requires further analysis.

As an example may be cited an experiment by Asher and Waldstein, the only uncomplicated one in which the duration of the diuresis is indicated. The blood of a rabbit fed on sago was transfused into one fed on hay and oats.

Time.	Urine.		
	Measured.	Calculated for 15 mins.	
9·58—10·8	4·8	7·2	—
10·14—23	8·5	14·1	10·11—10·14, transfusion of 65 grams of blood.
10·23—33	4·75	7·13	

It may be surmised that some constituent, perhaps urea, is present in unusual amount in the blood transfused from a starving animal, and that this acts as a diuretic. But as the concentration of the colloids in the plasma progresses, the glomerular filtrate lessens and the diuresis ceases. Until more is known of the constituents of the blood in starvation, it is impossible to discuss this point further, but it does not seem necessary at present to have recourse to the view that the presence of these unknown

substances in the plasma acts as a special stimulus to the "vital" secretion.

Asher and Waldstein found that transfusion from a starved animal to a fed one causes diuresis, while that from a fed animal to a starved one fails of effect, and conclude that in the starved animal the kidney is less capable of activity. But this does not follow immediately, for it is possible to explain the failure by the altered composition of the body fluids in starvation, which in animals generally leads to less water being taken.

Transfusion does not seem to affect the action of the diuretics of the purine group, such as theophylline; in some experiments they fail of effect, in others they have a very powerful action (Asher and Waldstein); the proportion of failures to successes does not seem to differ from that met in experiments without transfusion.

Serum Infusion.—Ponfick found that the intravenous infusion of lamb's serum into dogs caused no significant increase in the urine, even when an amount equivalent to more than one-third of the total blood was added. The amount of urine was not accurately measured, however, and lamb's serum is hæmolytic in the dog. In some experiments in which rabbit's serum was injected intravenously into another rabbit, I found a distinctly increased flow of urine follow (89). The animals had all been fed in the same way for one

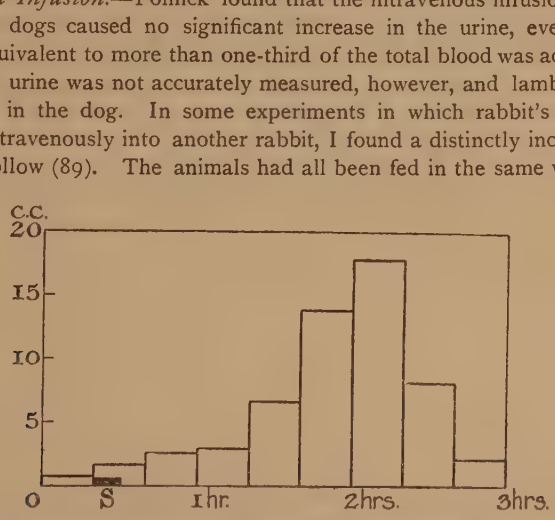

FIG. 19.—The course of secretion of urine after the injection of 40 c.c. of serum intravenously in a rabbit of 968 g. Time in hours.

or two weeks previously, so that the plasma in all had presumably a similar constitution. Such an injection was followed by a slow increase in the secretion of urine, which in one experiment reached its maximum only an hour and a half after the injection was finished (see Fig. 19). This is obviously an entirely distinct form of diuresis from that observed by Asher and Waldstein from the transfusion of blood from one animal into another in a different state of nutrition; for in their experiments the secretion rose abruptly and passed off very soon. The slowly increasing secretion from serum injection shows more resemblance

to that following a moderate injection of dilute sodium chloride solution and is probably identical in nature (see p. 127).

Defibrinated Blood.—The injection of defibrinated blood into the vessels has frequently been practised in experiments on the renal secretion, for example, by Goll (1854), who found that this restored to some extent the secretion which had been diminished by bleeding, and by Ponfick (1875), who found that it caused no change in the character of the urine. De Souza systematically defibrinated his dogs by repeated bleedings, whipping the blood and returning it to the vessels, and afterwards found the urine normal in character. Schwarz (1899) used the same method but states that the urine contained albumen afterwards, and his experiments indicate a very slow secretion. But Pfaff and Vejux-Tyrode found defibrinated blood by no means indifferent to the kidney of the dog; in their experiments blood was drawn repeatedly from the carotid artery, whipped, filtered, and allowed to flow into the jugular vein, about $\frac{1}{7}$–$\frac{1}{10}$ of the total blood being dealt with each time. Even a single withdrawal and reinjection of about $\frac{1}{10}$ of the total blood sufficed to change the character of the urine, which became scanty in quantity, amphoteric in reaction, and poor in urea. When the procedure was repeated, the urine contained much albumen, hæmoglobin, and red blood corpuscles, and the secretion ceased before the whole of the blood had been subjected to the treatment. But the condition rapidly returned to the normal, when the defibrinated blood was removed by bleeding, and fresh blood was transfused directly into the vessels from a normal dog. Barcroft and Brodie (1905) also find that defibrination in dogs impairs kidney secretion. The results of Pfaff and Vejux-Tyrode thus stand in direct antagonism with those obtained by De Souza, and doubtless by others whose methods have escaped my notice. It is possible that the discrepancy may have arisen from different methods being employed; at any rate the blood ought not to be defibrinated in further renal experiments, unless it is shown that it is less harmful than Pfaff and Tyrode found it. Coagulation may be prevented by leech extract apparently without damage to the kidney.

CHAPTER VIII.

BLOOD CONSTITUENTS AND THE SECRETION OF THE URINE —THE CHEMICAL FACTOR IN SECRETION.

General considerations—dilution diuresis and tubule diuresis—dilution diuresis—NaCl diuresis—NaCl by the mouth—bromide diuresis—water diuresis.

THE control of the renal activity through the blood supply, which has been discussed in the previous chapter, probably plays only a minor rôle under normal conditions, in which the variations in the circulation are smaller than those induced experimentally. The paramount influence determining the amount and composition of the urine in ordinary circumstances is the chemical constitution of the blood plasma.

A familiar example of the influence of the mechanical factor in health is offered by the lessened secretion of urine during sleep compared with that of the waking hours; this is apparently due for the most part to the lowered activity of the circulation during sleep. In disease, serious failure of the kidney occurs frequently from the mechanical results of heart failure. Examples of the potency of the chemical factor on the amount of the urine are seen in the diuresis after the ingestion of much fluid, and the deficient urine after the loss of water by perspiration or purgation. Its importance in the composition of the urine is manifested in the presence of innumerable foreign substances in the urine, as well as in the excretion of any excess of the normal constituents of the plasma.

This chemical factor received little notice from Ludwig in his earlier statements, and, as its importance was borne in upon him by later observations, he endeavoured to wrest his originally simple theory into some form in which this new feature might receive adequate recognition. But in the important paper by

Ustimowitsch from his laboratory, he practically abandons his previous standpoint, recognizing that the effectiveness of the blood pressure in regulating the secretion depends on the amount of the urinary constituents in the blood.

The importance of this factor in the regulation of the secretion of the urine has always been appreciated by the advocates of specific secretion, who have constantly pointed out the difficulties in bringing it into relation with the view of filtration and absorption. Their own statement is that excess of a normal constituent of the plasma, or the presence of an unusual body in it, arouses some renal cell to activity, which results in the expulsion of the intruding body and the return of the plasma to its normal condition. This "perhaps removes the blankness of ignorance, but conveys little of the illumination of knowledge," and utterly fails to account for some of the changes in the urine which accompany the disappearance of the foreign body from the plasma.

It may be remarked that, as in so many other respects, the kidney forms a contrast to the typical secretory gland in its ready response to changes in the composition of the blood (Asher (17)). This difference between the kidney and the liver or salivary gland in their reaction to changes in the blood supply and the blood composition has not been sufficiently recognized by those who still regard the process of secretion in all as essentially of the same nature, and this contrast in function may well be held to outweigh the resemblance in the histological characters of some of the cells in the kidney to those of the true glands.

The most striking effect of an abnormal composition of the blood is often the change in the amount of the urine, and this has been much oftener the subject of investigation than the proportions of the abnormal substance in the plasma and urine. It is therefore necessary to enter upon the labyrinth of saline diuresis in considering the influence of the plasma constituents on the secretion of the urine, and the actual changes in the proportions of the constituents in blood and urine can receive less attention in the present state of knowledge.

It has been pointed out in the statement of the modern view (p. 44) that the secretion of the urine may be influenced in two distinct ways by changes in the composition of the blood :—

1. The concentration of the colloids of the plasma may be changed, and with it the osmotic resistance to filtration through

the capsule. If the mechanical factor remains constant, lessened colloid concentration must therefore increase the filtrate, while any increase in the colloid concentration must diminish it. This may be termed the *colloid-concentration factor*, and the increase in filtration which follows a reduction in this factor will be called *dilution diuresis*. It is to be added that dilution diuresis does not originate in any action of the abnormal constituents on the kidney, but in their effects in the blood and general tissues.

2. If there is present in the plasma, and subsequently in the glomerular filtrate, any solid which cannot permeate into the epithelium of the tubules, it retards the absorption of the fluid in which it is dissolved and thus increases the urine. This I shall call the *permeation factor*, and the increase in the urine from the presence of non-permeating bodies in it will be spoken of as *tubule diuresis*. This form of diuresis, unlike that which is due to the mechanical or the colloid-concentration factors, arises from the relation of a substance to the renal cells directly.

In theory it is quite simple to keep the two forms of chemical diuresis distinct from each other and also from that arising from mechanical changes, but in actual experimental work this is more difficult, and indeed the separate existence of these factors has not been realized hitherto. Very generally two, or all three, factors are involved in the increase in the urine. The effects of changes in the colloid concentration can be studied only in the action of "threshold" substances, and the least complicated form is that afforded by the use of isotonic salt solution or Ringer's solution. Here the only difficulty is the frequent interference of mechanical changes, in the form of capillary distension. When "no-threshold" substances are injected in solution, the diuresis arises partly from these same mechanical and colloid-concentration factors and partly from the non-permeation, and the rôle of the last can be disentangled only by careful comparison of this complicated diuresis with that arising from simple dilution diuresis; this can be done only in the most general way in the present state of our knowledge. The dilution diuresis is common to both, and our rather scanty knowledge of the effects of changes in the colloid concentration can thus be supplemented.

Dilution Diuresis.

The diuresis from changes in the constitution of the blood may be complicated by changes in the renal blood supply, and it may therefore be well to clear the ground by considering how far these can be disentangled. The experimental evidence is rather unsatisfactory in spite of a large number of researches. The changes in the arterial blood pressure after saline injections are not important; it often rises after the injection of small quantities of saline which cause moderate diuresis (Knowlton), while it may fall in similar experiments (Thompson). Large injections often cause a fall in pressure, but not by any means always.

Starling (1899) in the important paper in which he showed the bearing of the colloid concentration on the process of capsular filtration, refers to dilution of the proteins as a cause of diuresis, and then devotes most of the rest of the paper to demonstrating that the chemical diuresis arises from changes in the blood supply (capillary pressure) of the kidney. With this object he used the oncometer, and his example has been followed by many later workers in the field. All agree with the results obtained earlier by Roy and Cohnheim, that during the diuresis from the intravenous injection of salt or sugar solutions the volume of the kidney increases to a marked degree, and that the course of the diuresis runs fairly parallel to the volume record. Some deviations were noted by Starling and these have been further developed by Thompson, Gottlieb and Magnus, Lamy and Mayer (1903, 1904), and others. From these experiments it has been inferred that in this form of diuresis the blood-flow through the kidney is greatly increased, and that the secretion of the urine, with some small deviations, varies with the blood-flow. But the oncometer record cannot be taken as an exact indication of the state of the vessels or of the supply of blood to the kidney during diuresis. For the kidney volume depends not only on the calibre of the blood vessels, but also on that of the renal tubules, and on the amount of lymph in the interstices. Now it has been shown beyond question that during diuresis the tubules are much wider than during less active secretion, and part of the increase in volume of the kidney must be ascribed to the dilated uriniferous tubules, and not to vascular dilation; how large a share of the increased volume should be referred to each of these is, of course, unknown.

When there is no secretion, the oncometer record may be taken to indicate the dilatation of the vessels directly, and it is therefore important to note that Schlayer and others have found that the injection of saline solutions increases the volume of the kidney, even when no diuresis follows owing to pathological conditions of the epithelia. These experiments show that the renal vessels are dilated when the total mass of the blood is increased by saline

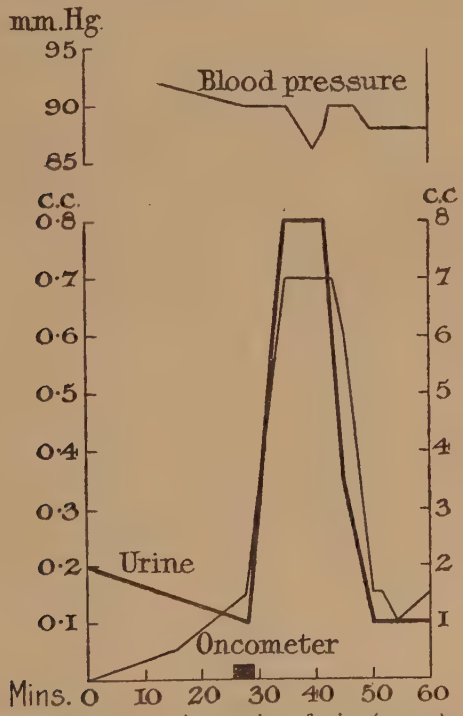

FIG. 20.—Oncometer curve (———), secretion of urine (———), and blood pressure (uppermost tracing) in a rabbit on the intravenous injection of 10 c.c. 10 per cent sodium chloride (■). The volume of the oncometer is given in the scale on the left, the secretion of urine on the right. (After an experiment of Gottlieb and Magnus.)

injections, but they do not, of course, prove that the diuresis corresponds in degree to the dilatation of the renal vessels; nor do they indicate in fact that the vascular dilatation is greater or more specific in the kidney than in other organs.

Alcock and Loewi state that when the kidney is embedded in gypsum and therefore cannot increase in volume, the injection of saline still causes diuresis; they infer that the vessels are

dilated because the venous blood becomes brighter in colour, but it is difficult to understand how the kidney can contain more blood and more urine and yet remain unchanged in size. If their method excluded an increase in volume, as they hold, the diuresis must have been independent of vascular dilatation.

The fact that the oncometer fails to record the blood-flow in the kidney during diuresis removes the cogency of a very ingenious experiment of Starling's. He argued that if the mechanical change in the renal circulation is solely responsible for the diuresis, the latter should not occur if the dilatation of the vessels is prevented. Accordingly, he repeated the oncometer experiment, but drew blood from the carotid in such quantity that no increase in kidney volume occurred, and found that no diuresis took place. (See Figs. 21 and 22.) He argued that since the diuresis can be abolished by nullifying

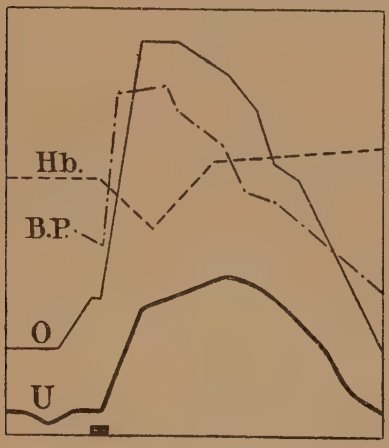

FIG. 21.

FIG. 22.

FIG. 21.—Graphs of secretion of urine (———), oncometer volume (———), blood pressure (·—·—·—·), and percentage of hæmoglobin in blood (- - - -) on the injection of dextrose solution in a dog. (Starling.)

FIG. 22.—Graphs as in Fig. 21, but here blood was drawn during the injection so that no rise in the oncometer tracing occurred. (Starling.)

the effect of the injection on the circulation through the kidney, there are grounds for concluding that the diuresis is due to the changes in the circulation. This experiment was criticized by Gottlieb and Magnus, who pointed out that more than half of the blood had to be drawn in order to prevent diuresis, and that this must have other effects than the mere reduction of the renal vaso-dilation. In order to meet this objection, I (89) modified Starling's experiment by maintaining the kidney volume constant by constricting the renal artery instead of drawing blood; the secretion from the two kidneys was then compared, the one being untouched, the other kept constant in volume by diminishing the arterial supply. The results were the same as

Starling's—when saline diuresis was induced and one artery was constricted so that the volume remained unchanged, the urine of that side did not exceed the normal amount, but it rose to 40-60 times as much when the artery was released. In Starling's experiment, the arterial blood pressure fell from 100 mm. to 60 mm. from the hæmorrhage, and in mine there can be no question that the pressure in the renal artery and therefore in the capillaries was similarly reduced, and this in itself would serve to invalidate the inferences drawn. But, in addition, the effect of the bleeding and of the constriction was to reduce the volume of the kidney until not only no vascular dilatation was present, but also no more fluid was in the tubules than before the injection; for if any abnormal secretion had occurred, the volume would have been increased. In short, these measures sufficed to arrest both the diuresis and the dilatation, and it was then argued that the diuresis ceased because the dilatation was absent. One cannot help regretting that an experiment that at the time seemed convincing, loses its cogency when subjected to closer analysis.

The apparent coincidence of the oncometer record with the diuresis must therefore be rejected as evidence of the dependence of the latter on the blood-flow through the kidney, and at the same time the divergence from the parallelism of the two records, which has been insisted on by Gottlieb and Magnus, Lamy and Mayer and others, loses its importance as an argument against this interdependence. The fact that the volume of the kidney increases under saline injection when diuresis is prevented by parenchymatous disease of the kidney (Schlayer), suggests, however, that this may be a factor in the diuresis.

Further evidence may be obtained by methods of measuring the blood-flow more directly. This was first attempted by Landergren and Tigerstedt by means of Ludwig's stromuhr, which was inserted in the renal artery; but the manipulation was fatal to the renal secretion, which is arrested by even a short interruption of the arterial supply, and they obtained no diuresis from saline injection, although here again the blood-flow was increased. Schwarz (1889) measured the outflow from the renal vein directly, and concluded that diuresis may occur without an increase in the blood-flow through the kidney. But his experiments are very unsatisfactory, as very little urine was passed in most of them, probably because he defibrinated his animals previously (see p. 118), and the outflow from the vein is extraordinarily low in all cases. In the only experiment in which there was a significant increase in the secretion, the blood-flow was doubled.

Barcroft and Brodie improved on Schwarz's method by

avoiding any interruption of the return flow through the renal vein. They inserted a cannula in the inferior vena cava below the renal branches, and thus could measure the outflow through the cannula at intervals, while normally the blood returned to the heart by its ordinary route. During saline diuresis there was sometimes an increase in the blood-flow, but this was by no means generally the case, and they conclude that increased rapidity of blood-flow through the kidney is not an essential feature of diuresis; when the blood-flow is increased, it invariably falls off much earlier than the diuresis, and it is never proportional to the amount of secretion; it may be added that in many of their experiments the diuresis was comparatively slight. Robertson observed acceleration of the flow through the kidney in saline diuresis.

More definite results were obtained by Lamy and Mayer (1906) by the use of Barcroft and Brodie's method of measuring the venous outflow from the kidney. They found that in the dog a large injection of salt solution accelerated the blood-flow and increased the urine, while a smaller injection did not accelerate the blood-flow but nevertheless caused diuresis; in both cases the blood was diluted, as was shown by estimations of the total solids. The following experiments are extracted from this important paper:—

EXPERIMENT 1.—*Dog of* 13·5 *kgs.*

Time after injection. Mins.	Water of blood, per cent.	NaCl of blood, per cent.	Blood-flow through kidney per min.	Urine in 10 mins.
—	82·6	0·55	150 c.c.	2·6 c.c.
Injection of 200 c.c. of 10 per cent NaCl intravenously.				
0-20	85·3	1·15	171·4 c.c.	16 c.c.
20-50	85·6	0·625	150 c.c.	7·3 c.c.
50-90	85·0	—	120 c.c.	2·25 c.c.

EXPERIMENT 2.—*Dog of* 14 *kgs.*

—	79·9	—	120 c.c.	1·0 c.c.
Intravenous injection of 100 c.c. of 10 per cent NaCl.				
0-15	82·4	—	92·3 c.c.	36·6 c.c.
15-45	81·3	—	80 c.c.	15·6 c.c.
45-95	80·7	—	63 c.c.	4·5 c.c.

In the second of these experiments, diuresis occurred though the blood-flow through the kidney was reduced, showing that the increase in the urine was independent of the mechanical factor. Barcroft and Straub in further experiments found that during saline diuresis the venous outflow was increased in the majority,

but not in all, at any rate in any significant measure. Thus the number of c.c. per minute was found in some of these experiments to be

Before diuresis . .	50	50	33	66	24	86
During diuresis . .	50	55	30	60	24	75

And Richards and Plant state that in their perfusion experiments diuresis was caused by the injection of 5 per cent salt solution without any change in the rate of flow through the kidney.

These all point to one conclusion—that while the diuresis from the intravenous injection of saline solutions is often accompanied by acceleration of the renal blood-flow, this is not by any means always true. Similarly, the arterial pressure sometimes rises, but frequently undergoes no marked change, or may fall during the diuresis. Thus the mechanical factor does not suffice to explain the saline diuresis, though it often co-operates with the chemical changes in the plasma to increase the secretion. The nature of these chemical factors is best shown by the diuresis following the injection of sodium chloride solutions and sodium sulphate solutions respectively.

Sodium Chloride Diuresis.

The injection of sodium chloride solutions intravenously is followed by an increase in the flow of urine; this occurs from solutions containing 0·4-0·9 per cent of salt, and also from hypertonic solutions; strong solutions act in smaller quantities than weaker ones; small amounts of isotonic salt solution have little immediate effect (Haake and Spiro).

If the quantity injected amounts to $\frac{1}{3}$-$\frac{2}{3}$ of the total quantity of the blood, the diuresis may set in only after half an hour or more, reach its maximum during the second hour, and then decline (Thompson, 1900); this form resembles that seen after the absorption of water from the alimentary tract, with which it is really identical in essential features. The time of onset and the extent and duration of the diuresis, however, vary with the rate at which the injection is made, the strength of the solution and its amount, and to some extent with the animal under examination. When large quantities are injected (Dastre and Loye, Magnus), the diuresis begins within a few minutes, increases as long as the infusion continues, and then falls slowly, the secre-

tion reaching almost normal dimensions in 3-4 hours. The amount of urine is extraordinary when very large quantities of saline solution are injected; for example, Magnus (241) obtained 725 c.c. in an hour from a rabbit into which he had injected 780 c.c.; the animal thus passed urine to the amount of 45 per cent of its total body weight in an hour. In fact, if 0·6-0·9 per cent NaCl solution is run into a vein slowly and continuously, an equilibrium tends to be established after a

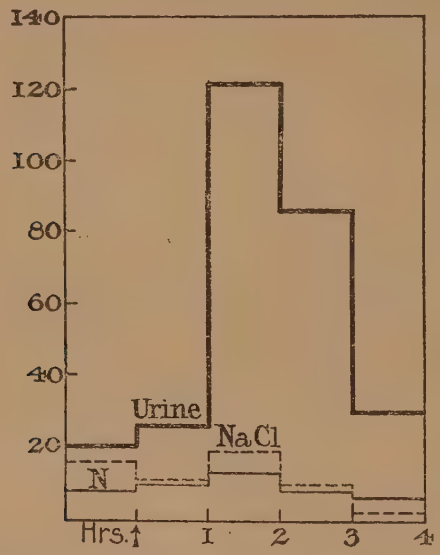

FIG. 23.—Graphs of the secretion of urine (——) and of total nitrogen(———) and chloride (- - - - -) in a dog. 40 c.c. (= 3 c.c. per kg.) of 0·9 per cent sodium chloride were injected intravenously at the point indicated with an arrow. (After Thompson's protocols.)

time, almost exactly as much fluid escaping by the kidneys as is injected (Dastre and Loye).

The diuretic action of saline injections has been examined in detail by Magnus in a very valuable paper (241). The experiments were performed on dogs in order to admit of an analysis of the changes in the blood as well as in the urine. The diuresis in these did not reach the height observed in the rabbit, but was very abundant. The injection is followed by a large interchange of water and salts between the blood and the tissues, so that the fluid is diluted not only by the plasma of the blood but practically by all the lymph also. The concentration of the

plasma reaching the kidneys thus lies between that of the normal plasma and that of the injected fluid.

When the infusion of saline is stopped, the diuresis lessens to same extent, and a counter-current from the tissues to the blood follows; but even after the urine has fallen to almost normal proportions, a large proportion of both the salt and the water injected is still retained in the tissues.[1] In Thompson's experiments with more moderate injections, the whole of the fluid was excreted in the urine. Magnus points out that the diuresis does not arise from the change in the concentration of the salts in the blood, for it occurs whether this is increased by the injection of hypertonic solution, decreased by hypotonic, or unchanged by an isotonic one. Nor is it caused directly by the increased mass of the blood, for it often continues after the total contents of the vessels have returned to the normal. And similarly, the percentage of chloride in the plasma may return to the usual before the diuresis ceases. He is thus inclined to ascribe the diuresis to the hydræmia, though he has some misgivings, because the diuresis sometimes ceased before the blood had regained its previous concentration of total solids. In his second paper (241) he withdraws from even this cautious attitude, and seems to regard the diuresis as the evidence of some specific stimulation of the renal cells.

This diuresis is readily intelligible, however, by the modern theory. For, as Magnus observed without appreciating its importance, the one feature common to all his experiments was a reduction in the concentration of the plasma proteins during diuresis;[2] examples drawn from his protocols are given in the table on next page.

With the fall in the concentration of the proteins and other colloids, the osmotic resistance to the filtration is reduced, and a copious flood passes through the capsule and into the tubules, corresponding in composition to the plasma in all points except the colloids. This excess of fluid puts the absorbing power of the tubules to the test, and its failure is conspicuous in the

[1] In these experiments with anæsthetized and therefore motionless animals, the conditions are very unfavourable to the return of lymph from the tissues; it may be doubted whether as much fluid would remain in the tissues in animals in a normal state of activity. It is probable that a larger proportion would escape in the urine.

[2] This may be accompanied by an actual increase in the total solids as Thompson observed.

rabbit, in which the urine comes to resemble the plasma in its content of chloride, sugar, and most other constituents. In the dog the absorption is more developed, but even here the flood is often too great to permit of complete elaboration, and some sugar may escape in the urine. The inefficiency of the absorption during the flood is further shown by the chlorides escaping in unsuitable concentrations. Thus very often when the chlorides were in excess in the plasma and their elimination was desirable, Magnus found the urine comparatively dilute, while when the plasma chloride was low, and the condition called for a large secretion of water, salt was eliminated in greater proportion than water, so that the diuresis actually made the general condition worse.

	Normal.		During Diuresis.		During Fall of Diuresis.		Fluid injected.
	Urine in 10 mins.	Plasma protein, per cent.	Urine in 10 mins.	Plasma protein, per cent.	Urine in 10 mins.	Plasma protein, per cent.	
Exp. 1	1·2 c.c.	7·33	11·5 c.c.	3·84	—	—	0·92 per cent NaCl
„ 2	1·0 c.c.	5·94	57·5 c.c.	3·17	4	4·57	0·6 „ „
„ 3	1·5 c.c.	4·43	62·5 c.c.	2·86	37	3·28	0·44 „ „

This disorganization of the reabsorption occurs only when the kidney is overwhelmed with a rapid infusion. It can be seen in some of Magnus' experiments, in which the fluid is injected more slowly, that the tubules are more able to cope with the flood of filtrate, for a larger proportion of the water or salt which is present in excess in the plasma, is got rid of with less loss of the other constituents. And even when extreme diuresis has been caused by a very rapid infusion, the efficiency of the absorption is shown to increase as the diuresis slackens.

The change in the amount of urine in Magnus' experiments is out of all proportion to the change in the concentration of the colloids, and in their osmotic resistance. Thus in Experiment 1 above, the urine increases nearly one hundred times, while the colloids fall less than one-half. Now the amount of the filtrate would be practically doubled by this reduction in the osmotic resistance, and the question may arise how this increase of 1 : 2 in the filtrate is reconcilable with an observed increase of 1 : 100

in the urine. Normally only a very small fraction of the filtrate escapes into the ureters, perhaps 1-3 per cent or even less (see p. 54), but during the flood, this fraction is greatly increased, and if it only reaches 50 per cent of the filtrate, and the latter is double the normal in amount, the urine will rise in the proportion of 1 : 100. It is not unreasonable to suppose that in the rabbit at the height of diuresis, an even larger part of the filtrate reaches the ureters—possibly 80-90 per cent—and in the dog also 50 per cent may be a high figure for the reabsorbed fluid during the flood stage.

As the diuresis passes off, the protein concentration in the serum rises, but this change is slower than that in the amount of urine, because the proportion of the filtrate which the tubules are capable of absorbing, rises as the total amount of filtrate falls, and the amount of the urine thus bears less and less proportion to the volume of the filtrate.

The importance of the failure of the absorption during the flood diuresis from saline infusion may be demonstrated in experiments in which the absorption is aided by partial closure of the ureter, which lessens the filtrate and thus allows the tubules more time to elaborate it (see p. 91).

In an experiment (89) in which a solution of 5·85 per cent sodium chloride was injected into a rabbit, and a resistance of 20 mm. of mercury was opposed to the escape of the urine from one kidney, the following figures were obtained during the diuresis :—

	Urine in c.c.	Chloride (Cl).	
		Gram.	Per cent.
Unobstructed side . .	17	0·1125	0·66
Obstructed side . .	5·5	0·0451	0·82
Difference . . .	11·5	0·0674	

In this experiment the blood obviously contained excess of chloride, but the kidney could only eliminate it with the loss of a large amount of water owing to the failure of absorption. When the absorption was artificially encouraged, however, the

percentage of chloride in the urine rose distinctly, that is, more of the water returned to the tissues, and the excess of chloride was eliminated at less cost in water to the organism.

The view that the lowered osmotic resistance to filtration is the ultimate factor in the sodium chloride diuresis, has received strong support from the experiments of Barcroft and Straub, who showed that the oxygen consumption is often not higher during this diuresis than in the resting kidney. This appears to prove that the actual work of the kidney is not increased, and precludes any "vital" secretion as the cause of the diuresis (see page 95).

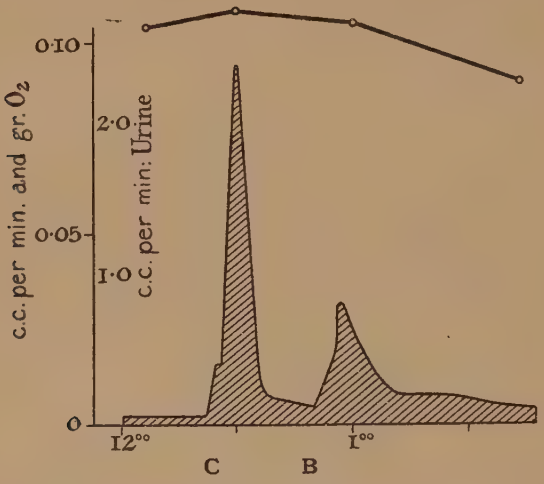

FIG. 24—The oxygen consumption (——) and the secretion of urine (dark areas) in Barcroft and Straub's experiment. At C a suspension of blood corpuscles in Ringer's solution was injected and caused marked diuresis. At B, blood was injected and caused much less change.

A still more crucial experiment is one in which these writers withdrew a certain amount of blood from a rabbit, removed the plasma by the centrifuge, and replacing it with Ringer's solution, injected this suspension of corpuscles intravenously. The secretion of urine rose at once to about 40 times the original rate (see Fig. 24). Here the only change in the conditions which could have caused the diuresis, appears to be the removal of a considerable proportion of the colloids of the plasma. The total bulk of the blood was unchanged, and the blood pressure was not increased but diminished, the saline injected only corresponded to the saline of the plasma withdrawn. Here also no increase

in the oxygen absorption occurred during the diuresis, and in the experiments of Winfield, which were of the same character except that very large quantities of Ringer's solution were injected, the oxygen absorption was even reduced during the diuresis to $\frac{1}{4}$-$\frac{1}{5}$ of the normal.

The chain of evidence appears to be completed by experiments in which salt solution was injected along with colloids, so that the osmotic resistance to the filtration was not reduced, although in other features the experiments were identical with those in which saline injections cause marked diuresis. Yet the addition of colloid was found to reduce or entirely abolish the diuretic effect. Thus Ponfick (1875) states that no diuresis follows the injection of a solution of salt containing egg albumen, although the quantity was larger than that used by Thompson to cause diuresis; and Moutard-Martin and Richet (1881) similarly found that the diuresis from the intravenous injection of sugar could be arrested by the injection of gum. But none of these attempted to explain their results, which was left to Knowlton in Barcroft's laboratory. He compared the diuretic effect of Ringer's solution alone with that of the same solution containing colloids such as gelatin or gum-arabic (Fig. 25).[1] The colloid injection uniformly caused less secretion of urine than the ordinary solution, though the effects on the blood pressure, on the blood-flow through the kidney, and on the oxygen consumption by that organ were the same from each solution. The only feature to which this difference can be attributed, appears to be the smaller reduction of the osmotic resistance of the colloids of the blood under gelatin saline than under saline alone.

The dilution of the proteins has another effect which has been observed frequently, and has generally been wrongly interpreted. In normal conditions of the blood, the kidney ceases to secrete when the blood pressure falls to about 40 mm. of mercury, because this is no longer sufficient to overcome the osmotic resistance of the blood colloids to filtration through the capsule (see p. 107). Under large injections of salines, however, secre-

[1] The kidney is not absolutely impervious to these, as it is to the blood proteins, for Spiro (1898) showed that gelatin passes into the urine and may even cause some diuresis; but the osmotic pressure measures not only the absolute but also the relative resistance to permeation, and this is certainly much greater in the case of these colloids than in that of the ordinary constituents of the urine.

tion continues at much lower blood pressures; this is well shown by injecting chloral along with the saline, when the blood pressure sinks continuously. Thus Gottlieb and Magnus observed secretion at a blood pressure of 13 mm., and Barcroft and Straub at 12 mm.[1] If the protein concentration is reduced to less than one-half the normal, as was the case in some of Magnus' experiments, the threshold blood pressure for secretion is also reduced in the like proportion, so that these observations offer no difficulty.

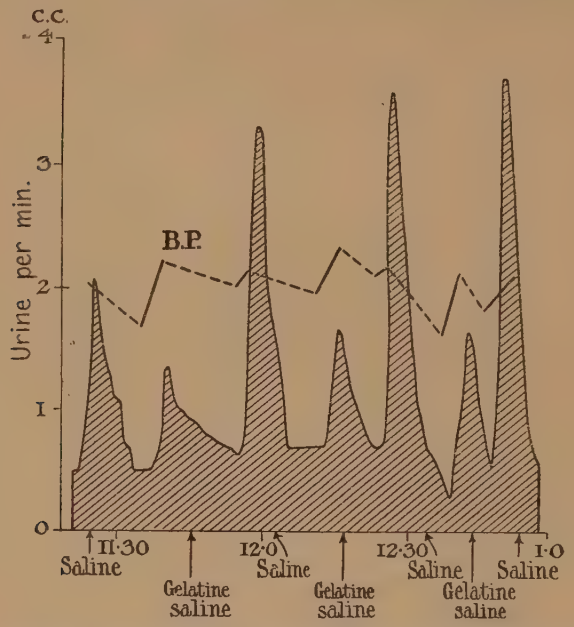

FIG. 25.—Knowlton's experiment. The broken line represents the blood pressure, the dark areas the secretion of urine under the injection of ordinary saline solution and saline containing gelatin alternately. The diuresis from saline alone is much greater than that from saline with gelatin.

It is probable that the pressure of secretion (see p. 109) rises on dilution of the blood for the same reason, the resistance to filtration being reduced and the pressure on the two sides of the capsule thus approaching each other. But the difficulties of the estimation and the changes in the capillary pressure have hindered this from being adequately examined.

The characters of the urine during dilution diuresis have been

[1] In their paper it is stated at 6 mm., but Dr. Barcroft informs me that this is an error. Similarly their 13 mm. should be 25 mm.

examined with some care, but differ only slightly from those obtained in urine in other forms of diuresis, so that the following may be taken as a description of diuretic urine in general. The urine in diuresis always approaches the plasma in composition more nearly than when the secretion is more moderate.

It is a clear, only slightly coloured fluid with a reaction distinctly nearer to the neutral than normal urine. The total concentration of the solids of the urine (Δ), as measured by the depression of the freezing-point, is lower during diuresis than in normal urine, but never falls below that of the blood at the time. The "no-threshold" constituents—urea, pigment, phosphates, sulphates—fall in percentage as the urine increases; but the total of each of these excreted in a unit of time is somewhat increased during diuresis. The potassium and the purine bodies are also increased in total amount, and also fall in percentage.

The reaction of the urine tends to approach that of the plasma during diuresis; thus the normally alkaline urine of the herbivora approaches the neutral, while the acid urine of man and the carnivora becomes less acid, or may even become neutral; when the herbivora have been induced by special feeding to pass acid urine, the reaction changes to neutral or alkaline during diuresis (Rüdel). This will receive further discussion in the chapter on acidity.

The change in the sodium and chloride of the urine during diuresis has been the subject of much discussion, and differs in different animals, as has been elaborated by Filehne and his pupils (289, 319). The urine is often richer in chloride than the plasma in normal animals, and during diuresis the chloride falls. When, however, the urine is poorer in chloride than the plasma, diuresis increases the chloride percentage in the urine, especially in the rabbit, in which flood diuresis is more easily obtained than in the dog, as has been stated. The total excretion of chloride in the urine per minute is increased in either case. When hypotonic solutions of chloride are injected, the concentration of chloride in the urine is generally lower than when isotonic or hypertonic solutions are used, but much depends on the rate of injection, the quantity, and other circumstances.

The sugar follows the same rule as the chloride. If it is present in the urine from hyperglycæmia, diuresis reduces the percentage and raises the total amount escaping, while if there

is practically no sugar in the urine, as in normal animals, diuresis may increase the percentage and the total amount. Glycosuria is very frequently present in the rabbit during well-marked diuresis (Bock and Hoffmann), while it only occurs in extreme diuresis in the dog, unless the sugar of the plasma is artificially raised in concentration. The glycosuria may pass off in the rabbit after very prolonged diuresis, from exhaustion of the glycogen of the liver.

In short, all the constituents of the urine are increased in absolute amount per unit of time during diuresis. But the "no-threshold" substances are invariably reduced in percentage, while the "threshold" substances are often reduced in percentage, but may actually rise in some circumstances. As the diuresis passes off, a change in the opposite direction sets in, the absolute values falling, while the percentage of the "no-threshold" bodies rises, and that of the "threshold" bodies may rise or fall according to the conditions.

This anomalous behaviour of the threshold substances has been the cause of much discussion, and even of some heart-burning (see the papers of Filehne and his pupils), and has been held to absolutely negative the filtration-reabsorption view. It is really entirely in accord with the modern modification of it. For the high percentage of chloride in the urine of animals fed with abundance of chloride and passing a normal amount of urine, arises from the tubules withdrawing from the filtrate the optimal fluid leaving the excess of chloride along with the urea, etc., and the water held back from absorption.[1] On the other hand, if the chloride of the food is deficient, the tubules, again subtracting the optimal fluid from the filtrate, leave only the urea and water with a trace of chloride. In diuresis, the too abundant filtrate is hurried through the tubules too fast for such complete elaboration, and the urine, therefore, approaches the plasma in its composition, containing a lower percentage of chloride than the previous urine if the latter was richer than the

[1] It is unknown how much of this chloride in the urine is in combination with potassium, which is reabsorbed only to a limited extent; it cannot exist except in association with an anion, and thus some of the chloride in the urine may escape absorption through being held back by the potassium ion. During diuresis from NaCl, the proportion of chloride retained as KCl would become comparatively small.

plasma in chloride, or more chloride than the previous urine in the opposite case.

The same holds true for sugar, which differs from chloride in its relation to the kidney only in the fact that in normal conditions its threshold is never reached, and thus it does not occur in the urine. The behaviour of sugar in NaCl diuresis thus corresponds to that of the chloride in animals in which the normal urine contains a lower concentration of chloride than the plasma ; that is, the percentage of sugar rises in the urine in diuresis in normal animals. When glycosuria is present, the relations are similar to those in which excess chloride is being excreted in the urine ; the percentage of sugar falls in diuresis.

The slight increase in the "no-threshold" bodies arises from the greater amount of filtrate and the greater movement and interchange between the plasma and the fluid of the tissues. This leads to some increase in the total amount of urea, etc., in the urine, but it is smaller than the increase in chloride, because urea is not normally reabsorbed, and impairment of the absorption, therefore, does not increase that escaping into the ureter.

The excretion of uric acid and potassium, the two constituents which appear to stand midway between urea and chloride in the height of their threshold, has not been very carefully examined during diuresis. Burian and Schur found that in the dog in some forms of saline diuresis the purine bodies are increased more than the total nitrogen and less than the water, which is what would be expected. But further research is required here. In the bird, Sharpe states that during diuresis the uric acid is increased in total but not in percentage, thus corresponding to the excretion of urea in mammals.

Here may be mentioned a view developed by Loewi (1902) which received a good deal of attention. He suggested that those bodies which increased in the urine during diuresis, escaped through the glomerulus by filtration, while those which did not increase, among which he placed sugar and phosphate, failed to do so because they were in colloid combination in the plasma, from which they could be freed only by specific secretory processes in the epithelium of the tubules. But Bock (1908) and Baetzner have shown that the total phosphate of the urine increases in diuresis in the same way as the total sulphate or urea, and sugar is free in the plasma. The increase in the phosphate in diuresis is small only, because its percentage in the plasma is very low, and since it is not reabsorbed in the tubules, the failure of the absorption does not affect it as the threshold bodies, chloride and water, are affected. The in-

crease in urea is more distinct, only because the latter is present in the plasma in larger proportions than the phosphate.

Sodium Chloride by the Mouth.

Sodium chloride taken by the mouth, even in considerable quantities, often fails to increase the urine in quantity, but appears in higher concentration in it. In other cases it causes diuresis without much rise in the percentage of chloride, while in still others, the urine increases in amount and also in its content of chloride. This variation probably depends rather on the condition of the tissues in general than on the reaction of the kidney to salt. In a cat whose urine normally contained 0·02-0·03 per cent chloride and 11-12 per cent urea, I found that 3 grams sodium chloride given by the mouth did not increase the urine of the next twenty-four hours, but the chloride rose to 0·2 per cent. Here in the normal condition, I take it, the plasma contained practically no more chloride than is contained in the optimal fluid, and the withdrawal of the latter by the tubules left merely a trace of chloride and a concentrated solution of urea to pass into the ureter. When chloride was supplied, the plasma containing excess, the filtrate contained more than could be withdrawn in the optimal fluid, and this remained along with the urea and water. A certain amount of water was held in the tubules, because their epithelium was unable to absorb against the osmotic pressure of the urea, and the chloride simply remained dissolved in this. On the other hand, if a very low percentage of urea is present, as occurs in the rabbit, chloride in excess in the filtrate and therefore not absorbable in the optimal fluid, may lead to the retention of water which would be absorbed otherwise, and the salt then leads to some increase in the urine.

In some cases of renal inefficiency, salt added to the food leads to dropsy, while a reduction in the salt may cause an increase in the urine and loss of fluid from the tissues (Widal and Javal). Here the effects of salt on the fluid exchange between blood and tissues may probably play a part, but the reabsorption in the kidney may also be involved. For if the glomerular filtrate is deficient, the water of the food passes out slowly, and the optimal fluid is very completely absorbed; if chloride is added, the filtrate approaches the optimal fluid more closely and more is absorbed, so that more fluid remains in the body, while if

the chloride is restricted, less of the filtrate will contain enough chloride to form optimal fluid, and thus less will be reabsorbed. If instead of chloride a no-threshold substance were given in these cases, one would expect that the oedema would be lessened, because the filtrate containing this substance would not be capable of absorption; and it is said that urea is of service in this form of renal inefficiency. This is an entirely hypothetical explanation, for the facts are still largely unknown. An interesting confirmation of it has appeared recently in a paper by Haldane and Priestley, who find that pure water in large quantities taken by the mouth does not lead to a dilution of the blood measurable by their methods, while Ringer's solution has this effect. Ringer's solution is practically optimal fluid, and this is largely reabsorbed in the tubules and is correspondingly slowly got rid of in the urine. Pure water, passing into the tubules as diluted optimal fluid, would lose its chloride very largely by absorption, but the excess water would not be reabsorbed.

The subcutaneous injection of sodium chloride solution has the same effect as the intravenous injection, except that the diuresis is often preceded by a stage of lessened secretion (Csernel, 1911), which is probably due to water being withdrawn from the blood to dilute the injected fluid; the concentration of the urine rises in this phase, as it does when water is withdrawn from the blood by other means, such as profuse sweating or purgation.

Bromides and Sulphocyanates.

The fate of the bromides in the body has been studied in late years by Wyss, Bonniger, Bernoulli, Frey (1910-11) and others, who agree in stating that most of the tissues, including the kidney, are unable to distinguish between bromides and chlorides, which therefore follow the same course in the body. When two substances resemble each other closely in their physical characters, such as solubility, diffusion, etc., they tend to accumulate in the same tissues in the body. Thus if a foreign salt resembling sodium chloride reaches a position normally occupied by the latter, a certain amount of exchange occurs, following the laws of mass-action, some of the chloride being expelled and replaced by the intruding salt. The more closely the latter

resembles the chloride in behaviour, the more extensive is this substitution, but many salts cause it in greater or less degree, and even other bodies, such as urea in all probability. The expulsion of chloride from the blood and tissue fluids occurs through the kidney. Other salts, such as sulphate and phosphate, which have less resemblance to chloride in their physical properties, have less tendency to displace it, and thus do not necessarily drive it into the plasma and urine. The administration of bromide has about the same effect on the kidney as the equivalent amount of chloride. The chloride in the plasma falls because some of it is displaced by bromide, and chloride and bromide appear in the urine in the same relative proportion as in the plasma. If the amount of fluid taken is low, the urine contains more chloride and bromide than the plasma, while in a more abundant flow the percentage of each falls below that of the blood; in respect to other forms of diuresis induced after the administration of bromides, the bromide elimination runs exactly parallel to that of the chloride. Bromide undergoes reabsorption in the tubules like chloride, and in fact the whole reaction is of interest only because the injected halogen can be distinguished chemically from that normally circulating in the blood. The excretion of bromide is extremely slow, traces being found in the urine up to two months after a single dose of a gram. Chloride administration accelerates its elimination in the same way as bromide increases the amount of chloride in the urine.

Sulphocyanates appear to resemble bromides in their behaviour in the kidney, replacing chloride in the same way and being reabsorbed in the tubules (De Souza, 1906-7). They do not appear to be retained in the body so long as bromide, however, so that they depart slightly from the chloride type, and form a transition between it and the nitrates (Sollmann, 1903).

Water.

The injection of distilled water into the blood is not followed by any immediate change in the activity of the kidney, as has been universally recognized.[1] After some hours a very slight increase in the urine may be observed. The reason is obviously that the water does not remain in the plasma, but immediately

[1] For example, Thompson (1900) observed no increase in the urine when distilled water was injected intravenously in amount equal to nearly one-third of the blood.

enters the blood corpuscles and other cells of the body, into which it is drawn by the high osmotic pressure in their interiors. If large quantities of distilled water are injected (e.g. up to 4 per cent of the body weight), the red blood corpuscles are laked and hæmoglobin appears in the plasma and ultimately in the urine.

Water injected into the subcutaneous tissues also fails to cause any immediate increase in the urine (Ginsberg, Cow, 1912), probably because the water is taken up immediately by the cells in the subcutaneous tissues and is only released slowly to the blood. After one to two hours a very slight, slow increase may begin. Water absorbed from the alimentary tract leads to an increase in the urine, which begins in about twenty to thirty minutes after it is swallowed, reaches its maximum in one to two hours, and falls slowly to the normal (Fig. 26), (Westphal).

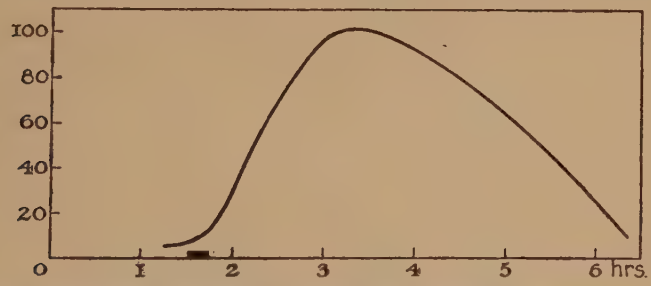

FIG. 26.—The excretion of water in periods of five minutes in man (3000 c.c. were taken at the point marked in the horizontal line). Time in hours. (After Priestley's protocols.)

Comparatively small amounts are sufficient to induce this; thus Hashimoto states that about 10 c.c. of water per kg. given by the mouth to a dog is sufficient to cause a definite increase in the urine.[1]

Large quantities of water taken by the mouth induce a profuse secretion of a very dilute urine, as is well known. For example, Dreser (98) found the total concentration of the urine sink after a litre of beer from a Δ of 1·5°-2·5° to one of 0·16°,

[1] The difference in the effect on the kidney of water given hypodermically and by the mouth has led Cow to suggest that in the latter case a ferment from the alimentary tract comes into play, but this is quite unnecessary and has been refuted by Hashimoto, who shows that as water is absorbed from the alimentary tract, it takes up salts and thus acts on the kidney in the same way as a dilute saline solution injected intravenously.

that is, to about one-tenth of the normal. And Macallum and Benson obtained a urine of $\Delta = 0.075°$, or only one-twentieth of the normal concentration, after drinking large quantities of water. The same result is obtained in animal experiments (Frey, 1907, p. 117). The specific gravity of the urine may fall from the normal of 1020 to 1001 (Haldane and Priestley).

In this dilute urine, the percentage of all the solids is much reduced, while the total solids and the absolute amount of urea, phosphate,[1] sulphate, and potassium excreted in a unit of time

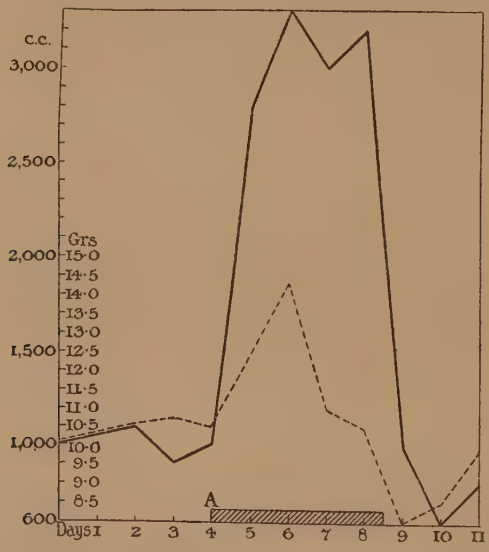

FIG. 27.—The influence of excess of water on the secretion of urine (——) and of nitrogen (- - - - -). A constant amount of water (1000 c.c. per day) was taken, but during the period marked on the abscissa 3500 c.c. were taken. (After a protocol of Neumann.)

is increased. The total amount of chloride excreted during the diuresis, as compared with that normally in the urine, depends rather on the richness of the tissues in salt than on the extent of the diuresis. It increases somewhat in the dog and often in man. The percentage of chloride falls, as is shown well in Loeb's observations (1906) on himself.

[1] Loewi's statement that the phosphate is not increased has been refuted by the careful work of Baetzner.

	Urine per min.	NaCl, per cent.	P_2O_5, per cent.
Previous urine	—	0·86	0·253
1000 c.c. of Water by the mouth.			
0-90 mins.	4·2	0·61	0·16
90-135 ,,	8·0	0·28	0·068
135-255 ,,	2·7	0·27	0·06

Macallum and Benson have drawn attention to the fact that the various solids do not show the same degree of change, the chloride falling more than the potassium during the diuresis and rising again more rapidly as it passes off.

This very dilute urine after water drinking has been a stumbling-block to the supporters of Ludwig's theory and a rock of offence to its critics, who have triumphantly pointed out that by no possible absorption of water by the tubules could urine more dilute than the glomerular filtrate be obtained, and that therefore specific secretion of water must be accepted. The views of the secretion school vary, some (Burian) believing that the glomerulus secretes a very dilute solution, others that the glomerular fluid remains unchanged after large draughts of water, but the tubules secrete additional water (Frey).

The reduction of the concentration is, however, not only compatible with the modern theory, but is a necessary element in it. The water absorbed from the alimentary tract reaches the plasma as a dilute saline solution and is rapidly carried to the kidney, where it is filtered off in a form slightly more dilute than the optimal fluid; the subtraction of the latter in the tubules leaves water containing urea and the other "no-threshold" substances, and such of the threshold bodies as are above the threshold (potassium and uric acid). Almost the whole of the chloride is reabsorbed in the optimal fluid, but some escapes.

A crude example may elucidate this. If the plasma is supposed to be diluted 10 per cent by the absorption of water, it may contain 100 c.c. water + 0·54 g. NaCl + Urea + Sugar. The optimal fluid will not amount to 100 c.c. for the 0·54 g. of NaCl is insufficient, and the amount absorbed is therefore 90 c.c. + 0·54 g. NaCl + Sugar, leaving 10 c.c. of water with practically no chloride or sugar, but at least the normal amount of urea in low

concentration. The example is crude and only intended to illustrate the principle. For it has been shown by repeated observations (Engel and Scharl, Macallum and Benson, Haldane and Priestley) that the dilution of the blood is extremely small even when 3 litres or more of water are taken. In fact it is so small that it cannot be recognized by the ordinary methods of examining the blood, though Priestley detected a change in the electrical conductivity. This, of course, does not show that the plasma is not diluted, but merely demonstrates the extreme sensitiveness of the kidney (and the epithelium of the tubules in particular) to changes in the concentration. The kidney is a much more accurate gauge of changes in the condition of the blood than the hæmocytometer or the refractometer of the laboratory. It is interesting to note that Priestley found that a dilute solution of salts similar to Ringer's solution caused more prolonged but less intense polyuria than an equal amount of water, and the blood dilution was shown here by the hæmoglobin estimation. Here, I take it, the filtrate corresponded to the optimal fluid more closely than when water was drunk, and more of it was reabsorbed, so that the excretion was delayed.

Several objections have been raised to this view of water elimination, chiefly because there has been a tendency to regard the excretion of water by the kidney as something apart from that of the other constituents of the urine. This, of course, is unjustified, for excess of water is got rid of in exactly the same way as excess of chloride or sugar or urea. Others have objected that when such immense quantities of urine are secreted, the absorption in the tubules must necessarily be imperfect owing to the flood diuresis, which is invoked by the modern school in experiments in animals. Thus Macallum states that after large draughts of water, he secreted urine at the rate of 20 c.c. per minute with a Δ of 0·075°, and considers that if the filtration-reabsorption view were correct, the Δ should have been approximately that of the plasma. I have no desire to depreciate his performance, with which he has every reason to be satisfied, but it fades into insignificance when compared with that of the rabbit, in which the failure of the absorption through overflooding from the capsule is best seen. For example, Magnus' rabbit (p. 128) secreted 12 c.c. of urine per minute, and its weight was 1·5 kg.; Macallum may weigh about 100 kg., and to rival the rabbit ought

to have produced not 20 c.c. per minute, but 800 c.c.; his urine might then have shown the same evidence of the escape of chloride, from failure of the absorption owing to flooding.

It is a question whether this flood diuresis can occur in man from water or salt solution taken by the mouth, for the absorption from the intestine is too slow. At any rate no evidence has been brought forward of its occurrence. Even in animal experiments, I have been unable to find any true flood diuresis from water given by the mouth, and Frey (125, p. 66) states that in the rabbit the administration of water by the mouth is followed by urine of $\Delta = 0{\cdot}1°$, so that even its feeble power of absorption is sufficient to save the optimal fluid.

Some experiments of Allard, in which the flow through the ureter was partially obstructed during water diuresis, have already been shown not to be opposed to the modern view, as he supposed (see p. 92).

CHAPTER IX.

BLOOD CONSTITUENTS AND THE SECRETION OF THE URINE (*continued*).

Tubule diuresis — sulphate diuresis — phosphates — nitrates — iodides — potassium — urea — sugars — general remarks on chapters viii. and ix.

THE diuresis from the presence of "no-threshold" bodies in the tubules which restrict the absorption of fluid, is almost always accompanied by reduction of the colloids of the plasma, and thus the tubule diuresis is not seen in a pure form, but is complicated by the dilution diuresis described in the last chapter. Perhaps unmixed tubule diuresis is best seen under urea given by the mouth in the dry form, or under sugar in diabetes, but these have not been exhaustively followed. The form of diuresis more frequently examined is that induced by the intravenous injection of solutions of the no-threshold bodies such as the sulphates.

Sulphate Diuresis.

Sulphates administered in quantity by the stomach are absorbed with difficulty and give rise to purgation, so that no diuresis follows. When injected intravenously, sodium sulphate causes a more abundant diuresis than the equivalent amount of chloride (Magnus (241), Sollmann, 1901). The urine rises in amount more rapidly, attains its maximum sooner, and often remains at this point longer, and then sinks more slowly, only reaching the normal after many hours. The contrast in the secretion is shown in Fig. 28.

The urine shows the typical diuretic characters, being abundant, clear, of low specific gravity, and of lessened acidity in the dog. The chloride percentage may rise during the height of diuresis, especially in the rabbit fed on salt-poor food, but may fall from

the beginning, if the diet has been rich in salt previously. In any case, it is very low in the later stages of diuresis, thus forming a contrast to the urine in chloride diuresis; the total chloride is increased during the very active diuresis, but also falls below the normal later. The sulphate percentage is high from the beginning and goes on rising as the diuresis passes off; the total sulphate is highest during the early stage, and falls as the urine diminishes. In the rabbit, sugar is often excreted during sulphate diuresis.

The difference in the action of sulphate and chloride injection does not appear to be due to differences in the mechanical con-

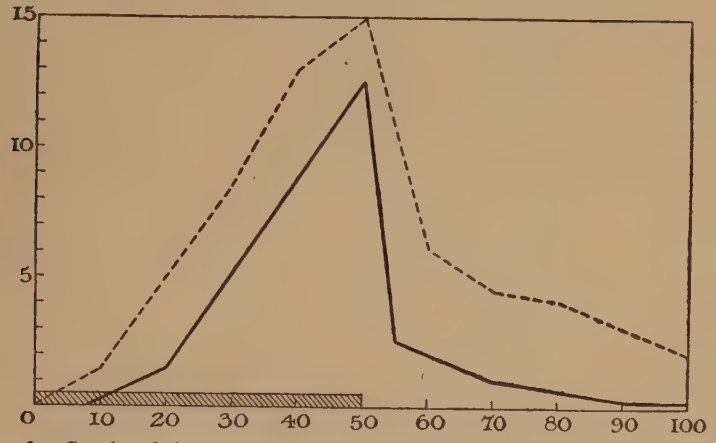

FIG. 28.—Graphs of the secretion in two rabbits after the intravenous injection of equal amounts of isotonic solutions of sodium chloride (——) and sodium sulphate (- - - -) respectively. The time of injection is indicated on the base line.

ditions of the diuresis under each, for the changes in the blood pressure are similar, and from sulphate the oncometer shows no greater increase in volume, but rather a smaller change (Gottlieb and Magnus (140)). No exact comparison of the blood-flow through the kidney under sulphate and chloride diuresis is available, and indeed it would be a tedious investigation, for each would have to be injected into a series of animals and the blood-flow in each series compared statistically. But there is no reason to believe that the blood supply to the kidney differs in relative proportions under sulphate and chloride diuresis, and the oncometer experiments, as far as they go, suggest that the circulatory conditions are rather more favourable under the chloride,

in which the diuresis is the slighter. Bainbridge and Evans showed in a perfused living kidney that sulphate causes diuresis without any change in the rate of blood-flow through the organ.

The hydræmia is not greater under the sulphate than under the chloride at the height of diuresis, and in the later stages the blood may even be more concentrated than normally, though diuresis continues (Magnus). This eliminates the colloid-dilution as the cause of the greater diuresis. Similarly the molecular concentration of the blood, as measured by the depression of the freezing-point, is not greater under the sulphate than under the chloride, and the chloride percentage of the blood actually is lower than usual, although of course there is excess of sulphate. Altogether the state of the blood does not suffice to account for the difference in the diuretic efficiency of chlorides and sulphates, and Magnus recognizes that the cause of the difference is some factor acting in the kidney itself. Gottlieb and Magnus regard this as evidence that sulphate stimulates the secretory cells of the kidney more than chloride.

A physical explanation of the greater diuresis under sulphate than under chloride was given by me in 1902, in a paper in which I showed that the relative proportion of sulphate and chloride in the urine is independent of their concentration in the plasma. This is seen in the following comparison of the serum and urine in rabbits at the beginning and end of diuresis :—

	During Diuresis.		After Diuresis.	
	Chloride, per cent.	Sulphate, per cent.	Chloride, per cent.	Sulphate, per cent.
Serum . .	0·547	0·259	0·493	0·191
Urine .	0·372	0·546	0·094	2·0

Sollmann (353) gives an experiment on the dog which agrees with my results in all essentials. In the experiment cited above, the plasma during diuresis contained more chloride and sulphate than later as the diuresis ebbed ; the chloride percentage fell in the urine, but that of the sulphate actually rose in spite of the relatively small concentration in the plasma. The sulphate thus offers a contrast to the chloride in its behaviour, and this I attributed to the sulphate failing to be reabsorbed in the tubules, while the chloride permeates readily. The evidence for this

difference in absorption will be given after it has been explained how it affects the diuresis.

The first stage of very rapid diuresis from sulphate arises from the colloid-dilution and the increased flow through the renal capillaries, which both accelerate the filtration through the capsule. The flood of filtrate can only be partially elaborated by the epithelium of the tubules, and much chloride and water are lost into the ureters. Even here, however, a certain absorption goes on, for the sulphate in the table above rises from the 0·259 per cent of the plasma (and of the filtrate) to 0·546 per cent in the urine, while the chloride falls from 0·547 per cent to 0·372 per

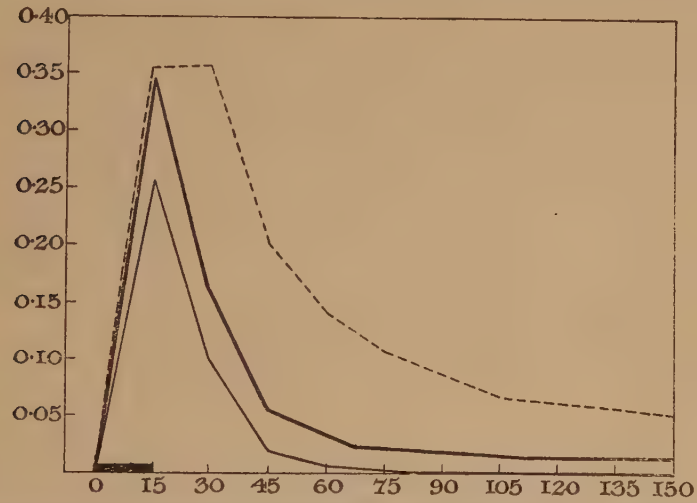

FIG. 29.—Curve of elimination of chloride (——) and sulphate (- - -), when they are injected together in equal amounts in a rabbit. Time in minutes. Urine (——).

cent in the urine. The absorption is less than it would be under chloride alone, because the sulphate cannot permeate the epithelium and therefore offers resistance to the absorption of fluid.

As the flood abates, this factor comes more into evidence; absorption becomes more complete, but cannot remove so much of the filtrate as in chloride diuresis, because the unabsorbable sulphate always limits the reduction of the fluid below a certain level by offering osmotic resistance. The sulphate diuresis thus lasts longer than that from chloride, and tails off very slowly as the sulphate is eliminated from the body (Fig. 29).

The chloride absorption is not prevented by the presence of

sulphate, like that of the water. And a certain amount of chloride has been lost in the first flood, so that after this has passed, the plasma and filtrate are rather poorer in chloride than normally; the abstraction of the optimal fluid by the tubules thus leaves a urine poor in chloride and containing a high percentage (2-3) of sulphate.

In support of the view that chloride is more readily absorbed than sulphate, three separate sets of experiments may be quoted, in each of which the effort was made (often unwittingly by the investigator) to inject sulphate without causing flood diuresis. The first of these was my experiment (1902), in which a mixture of sulphate and chloride solution was injected, and the outflow from one ureter was retarded by a mechanical resistance, while the other kidney secreted freely; the ratio $\frac{\text{chloride}}{\text{sulphate}}$ on the obstructed side was much smaller than on the free side.

Thus in an experiment on a rabbit in which one ureter was obstructed by a resistance of 30 mm. of mercury, while the other was free, the following results were obtained during the height of diuresis:—

	Urine in grams.	Chloride in grams.	Sulphate in grams.
(*a*) Unobstructed side . .	24	0·0809	0·1080
(*b*) Obstructed side . . .	8	0·0142	0·0667
Difference	16	0·0667	0·0413
Proportion of $\frac{b}{a}$ . . .	33 per cent	18 per cent	62 per cent

The filtrate must have been of identical constitution on the two sides, for the same blood passed through the two kidneys. Yet the obstruction lessened the chloride more than the fluid and still more than the sulphate. This could only be due to changes incurred during the passage along the tubules, that is, chloride was absorbed in larger measure than sulphate. The effects of obstruction of the ureter have already been discussed (p. 88), and it need only be stated that the modern view holds that the filtrate is diminished in quantity but is unaltered in quality; the obstruc-

tion in fact reduces the effect of the hydræmia and the mechanical factor, while leaving the absorption unaffected.

My results from obstruction of the ureter in sulphate diuresis have been confirmed in the main points by Filehne and Ruschhaupht (1903), and this is of the more importance as these authors are by no means favourable to the filtration-reabsorption view.[1]

Before considering the criticisms against this explanation of the effects of obstruction in sulphate diuresis, it will be convenient to follow a second path which also leads to the same interpretation. The diminution of the filtration by obstruction leads to a lessened excretion of water and chloride, while the sulphate undergoes less change. What would be the effect of lessening the filtration by constricting the renal artery? This has been determined by Yagi and Kuroda in a paper from my laboratory, in which they state that when the blood-flow is lessened by constriction of the renal artery on one side, the sulphate excretion is less diminished than the chloride or water on that side. For example, in an experiment on a rabbit with compression of the left renal artery and injection of a mixture of sulphate and chloride of sodium, they observed the following proportions in the urine of the two sides at the highest diuresis :—

	Urine in grams.	Chloride in grams.	Sulphate in grams.
(*a*) Normal side . . .	9·5	0·038	0·105
(*b*) Constricted side . . .	2·15	0·005	0·035
Difference	7·35	0·0325	0·070
Proportion $\frac{b}{a}$ . . .	22·5 per cent	14·5 per cent	66 per cent

Similar results were obtained when the blood-flow through the kidney was lessened by cardiac inhibition, while increasing the blood-flow led to the opposite result, the sulphate falling in percentage while the chloride rose. The reduction of the filtrate by restriction of the blood supply then has the same effect as

[1] Filehne and Ruschhaupt used solutions containing much less sulphate than in my experiments, and the diuresis must have been due in larger part to the chloride than to the sulphate; that is, the filtrate was richer in chloride and poorer in sulphate, and the absorption in the tubules did not reduce the chloride percentage so much.

its reduction by increased resistance to its escape by the ureter; the epithelium of the tubules, no longer overwhelmed by the flood of filtrate, can elaborate it more completely, and does this by withdrawing the optimal fluid, the chloride and water.

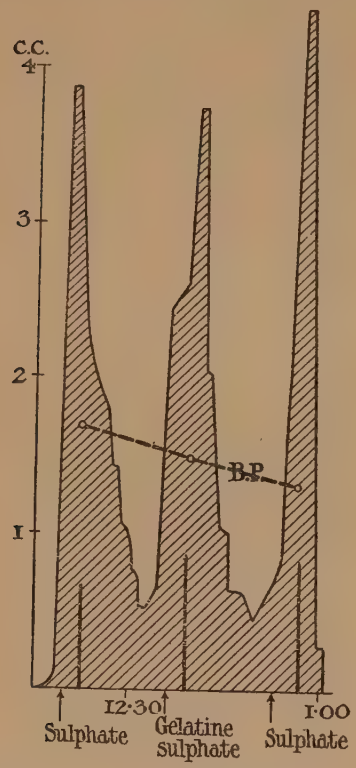

Fig. 30. — Knowlton's experiment in which the effects of sodium sulphate solution alone and with gelatin were contrasted. The addition of gelatin had very little effect on the diuresis (compare Fig. 25, p. 134); the flow of urine is indicated by the dark areas.

Exactly the same activity sets in when the flood passes off in the normal kidney under sulphate diuresis, and the result is the same—the urine becomes less abundant and the chloride sinks even more rapidly than the water, while the sulphate falls more slowly and actually rises in percentage, just as it does when the flood is artificially lessened by ureter obstruction.

A third line of investigation has been followed by Knowlton, who compared the effect of injecting small quantities of sulphate dissolved in water with that of the same quantities dissolved in gelatin solution; the effect of the gelatin is to prevent, to a considerable extent, the dilution of the colloids of the plasma and thus to lessen the dilution diuresis (see p. 133). He had previously shown that the addition of gelatin to chloride solutions injected intravenously prevents the diuresis, but this failed in the case of sulphate diuresis (Fig. 30), showing that the diuresis from small quantities of sulphate is not due to the mechanical factor or to dilution of the plasma but to some action in the kidney itself. Unfortunately, he neglected to estimate the amount of sulphate excreted in the urine.

The inferences drawn from my experiments with obstruction of the ureter on one side have been subjected to a somewhat severe criticism by

Filehne and Ruschhaupt (1903) and by Brodie and Cullis (1906), and as these criticisms have been regarded by their authors as definitely refuting the view of absorption of water and chloride in the tubules, they have to receive consideration.

Filehne and Ruschhaupt obtained similar results to mine in a number of experiments conducted in the same way. When, however, they first "enriched" their rabbits by an intravenous injection of strong sodium chloride solution, and allowed the resultant diuresis to begin to ebb before injecting sulphate, their results were discordant. On the obstructed side the urine was diminished in volume, but the percentage of chloride and sulphate was higher than on the free side. Here the chloride does not seem to be taken up by the tubules any more than the sulphate ; the reason is not far to seek. For the animal's tissues were rich in sodium chloride and poor in water from the previous diuresis ; it would have secreted a urine with high sodium chloride percentage if left to itself, that is, the tubules, taking out of the hypertonic filtrate the ordinary optimal solution, would have left the excess of chloride to find its way into the ureters. Now a new flood of filtrate reaches the tubules from the sulphate injection, but on one side the passage is slowed by obstruction of the ureter ; on this side absorption is more possible than on the other, and the result is that the optimal fluid is absorbed in large quantities, leaving the excess of chloride to issue by the ureter along with the concentrated sulphate ; the water alone falls in amount. That this is the true explanation of Filehne and Ruschhaupt's observations is shown by the fact that in two experiments in which large amounts of dilute sodium sulphate were run in continuously, the percentage of chloride on the obstructed side finally fell well below that on the free side. Here the chloride concentration in the plasma and filtrate had apparently fallen below the normal ; the tubules on the obstructed side thus absorbed from it more chloride than water (as was universally the case in my experiments), and the urine was low in chloride and high in sulphate. These experiments are therefore quite compatible with the view that the tubules absorb, as far as is possible, a dilute solution of sodium chloride ; I quite acknowledge that they are opposed to any idea that the epithelium takes up any and all chloride offered to it whatever its concentration, but this is no part of the modern view.

The experiments of Brodie and Cullis also agree perfectly with the modern view, though these authors regard them as negativing Ludwig's theory. They used dogs in which the central nervous system had been destroyed above the medulla oblongata, and gave no anæsthetic during the observation. The urine of the side on which the ureter was obstructed was often more abundant than that on the free side, presumably from the survival of some dilator reflex (see p. 12).[1] In practically all of Brodie and Cullis' experiments, the chloride was present in higher percentage in the more

[1] Brodie and Cullis believed that the slight pressure of 10 cm. water in their experiments was sufficient to excite the renal cells to higher effort. But this is quite untenable, for they themselves calculate that these cells are secreting against an osmotic pressure of 4-7 metres of mercury; yet they suggest that an additional pressure of 7 mm. mercury suffices to double their activity.

abundant urine, while the sulphate percentage was lower in it than on the side on which the secretion was smaller. This is exactly in accordance with my observations; the smaller amount of filtrate was more exposed to the tubules, and more of its water and chloride were withdrawn than was possible in the case of the more rapidly passing, abundant filtrate. Their observations are thus not opposed to the modern view, but entirely in accord with it, for the method of varying the rate of flow along the tubules is indifferent. Only the effects of the tardy flow are significant, and those observed by them are the same as those previously described by me.

Phosphates and Ferrocyanides.

Phosphates taken by the mouth are absorbed with some difficulty by the intestine and do not cause much diuresis. Injected intravenously, they induce diuresis of precisely similar character to that following sulphate injection, and they also resemble sulphates in their elimination in the urine when the outflow by the ureter is obstructed (88, 89).

Ferrocyanide appears to resemble phosphate and sulphate in its behaviour (Sollmann, 1903).

Nitrates and Chlorates.

Nitrates have long enjoyed a reputation as diuretics in clinical practice. They are absorbed fairly readily from the intestine, but no satisfactory estimate is available of their effect when administered in this way compared with other salts. Limbeck assigns sodium nitrate a position near the chloride in his list, but his method was very imperfect, solutions of salts of equal percentage being given without reference to their molecular weight. Injected intravenously, the nitrate is also assigned rather a low position by Munzer, but his technique leaves something to be desired, and he also compared percentage solutions of different salts, which of course gives little clue to the real activity of the ions. Haake and Spiro (1902), in their careful experiments, found that isotonic nitrate solution injected intravenously was much more effective than chloride, and in fact approached and sometimes surpassed sulphate solution.

Loewi (1902) observed diuresis from the intravenous injection of nitrate, which resembled that from phosphate, except that the chloride excretion in the urine remained high under nitrate, while it fell to a minimum in the later stages of phosphate diuresis,

as has been described under sulphate. And Sollmann (1903, p. 425) confirms this, finding that nitrate injection increases both the percentage and the absolute amount of chloride in urine previously poor in chloride, while sulphate tends to lower the percentage even while increasing the absolute amount of chloride. There seems no question that under nitrate diuresis a larger excretion of chloride in proportion to the other constituents occurs than under sulphates. Loewi ascribes this to the nitrate dislodging the chloride in the tissues and thus increasing its partial pressure in the blood; and Langlois and Richet have shown by actual analysis that the chloride of the tissues falls under nitrate treatment. In other words, the nitrate, like the bromide, is not differentiated from the chloride by many tissues, and these exchange part of their chloride for nitrate.

The nitrate appears to differ from the bromide in that the percentage in the urine rises with the ebbing of diuresis, while that in the serum is falling. Thus in an experiment of Sollmann's, the percentages of chloride and nitrate in the serum and urine showed the following variations:—

Time after Injection of Nitrate.	Urine in 10 mins. in c.c.	Percentage Nitrate in		Percentage Chloride in	
		Serum.	Urine.	Serum.	Urine.
1 min.	—	0·261	—	0·37	—
10 mins.	23	—	1·481	—	0·40
15 ,,	—	0·219	—	0·38	—
24 ,,	20	—	1·572	—	0·38
42 ,,	27	—	1·679	—	0·37
1 hr.	25	0·122	1·836	0·43	0·35
2½ hrs.	10	0·146	1·707	0·48	0·26

In bromide diuresis the proportion of bromide and chloride in the urine is practically the same as that in the blood, while in nitrate diuresis this does not hold, the nitrate in the urine rising while the chloride falls, and while the nitrate in the blood serum is actually falling also. In this respect the nitrate rather resembles the typical effect of the sulphates, from which it differs, however, in the latter inducing a smaller chloride excretion at the height of diuresis and also during the ebb. From these facts it may be suggested that nitrate is not differentiated from chloride in some tissues of the body, perhaps in most, and thus displaces the chloride from them, and leads to an increase in the chloride

of the urine. In the kidney tubule, however, the nitrate is not reabsorbed, and thus accumulates in the urine in increasing percentage. In other words, while nitrate passes instead of chloride in some tissues, its imposture is detected by the epithelium of the renal tubules. Bromide, on the other hand, escapes its vigilance, and sulphate deceives neither the kidney nor any other tissue.

Chlorates.

The course of the diuresis under chlorate has been examined by Ercklentz, and his results seem to indicate that the relations of the chlorates to the kidney are very similar to those of the nitrates.

Iodides.

Sodium iodide appears to resemble sodium nitrate in its relations to the kidney, for it increases the chloride excretion considerably, and thus appears to displace chloride from the tissues (Sollmann, 1903), while it increases in concentration in the urine as it diminishes in the serum during the ebbing of diuresis (Loewi, 1902, Frey (128)).

Potassium.

The relations of the potassium ion to the kidney have been examined in a very interesting paper by Bock (1907). He injected an isotonic (1·1 per cent) solution of potassium salt intravenously in rabbits at a very slow rate, so that there was practically no hydræmia, the solution being eliminated from the vessels about as rapidly as it was injected. A moderate diuresis occurred during the injection (see Fig. 31), the urine containing a high percentage of potassium and a slightly increased percentage of sodium. At the end of the infusion, the secretion fell to a very low point, and with it the excretion of sodium and potassium. But two hours later the secretion of urine again rose to a considerable height, while the potassium and sodium fell in percentage. During the first diuresis, the increase in sodium appears to be of the same nature as the increase of chloride when bromide is given, and the inference is that potassium displaces some of the sodium in the tissues and thus increases its concentration in the plasma and filtrate; for the rise in the urine is not enough to suggest that absorption was rendered imperfect by flooding. The

concentration of potassium in the plasma and filtrate was of course much lower than that of the sodium, for the former is highly poisonous to the heart in anything over about 0·05 per cent; on the other hand, the potassium in the urine was in much higher percentage than the sodium, and this can only mean that potassium is not reabsorbed by the tubules to the same extent as sodium.[1]

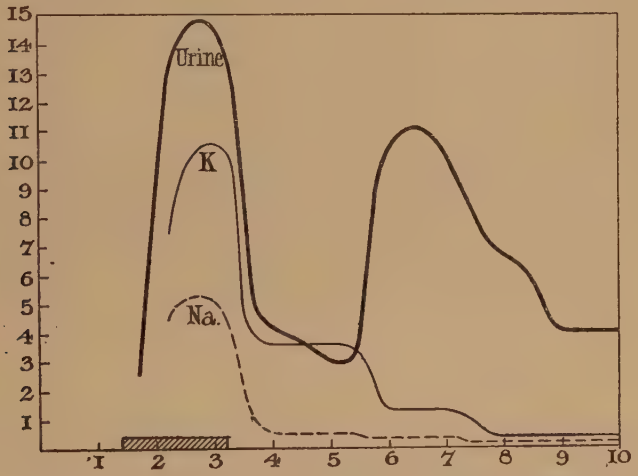

FIG. 31.—The secretion of urine (——) and the elimination of potassium (——) and sodium ions (- - - -) in it after the injection of small quantities of potassium sulphate intravenously in a rabbit. Time in hours. (After Bock's protocols.)

The primary diuresis appears to be of the same nature as that of the nitrate, the absorption through the epithelium being limited by the osmotic resistance of the potassium. This diuresis was insufficient to remove the water injected, which had escaped into the tissues and which gave rise to a late diuresis of the same nature, as is seen after the injection of moderate amounts of normal saline (Thompson). At this time the potassium had been elimin-

[1] This difference in the absorption (i.e. diffusion) of potassium and sodium is so unpalatable to Bock that he is driven to the view that the salts are subject to a specific secretion in the kidney. But this is merely changing from one horn of the dilemma to the other, for the secretory cell must also differentiate between the two ions, and it is no more difficult to believe that a cell absorbs sodium and rejects potassium than it is to accept that a "vitally secreting" cell accepts potassium and excretes it, while it refuses sodium and allows it to remain in the blood. The kidney undoubtedly differentiates between these two ions, and whatever view of its activity is accepted, it involves the selection by some cells of one of them in preference to the other.

ated for the most part, and the filtrate was unduly dilute owing to the loss of sodium in the first phase.[1] The urine in the second phase of diuresis thus contained practically only the excess of water. This second phase seems unduly delayed in all of Bock's experiments, perhaps from some toxic action of potassium on the heart in its previous stages.

The potassium ion thus resembles the nitrate and iodide in its relation to the kidney. The combinations of potassium and these anions are absorbed from the bowel almost as readily as sodium chloride, and their smaller tendency to be reabsorbed in the tubules makes them more efficient diuretics. The nitrates and iodides of the alkalies have long had a reputation as diuretics in medicine, and the potassium salts have been regarded as superior to the sodium salts. In this case, as in so many others, empirical therapeutics has advanced far ahead of the halting progress of scientific theory, and it is pleasant to find in Bock's work an adequate explanation of the clinician's empirical view.

Urea.

Urea has long been known to have diuretic properties of some value, and has been in use in therapeutics either as such or in the guise of salts, such as ammonium acetate or citrate, which are decomposed in the tissues with the formation of urea.

Injected intravenously, its action on the kidney is less marked than that of the sulphates. Urea diffuses readily into red blood cells, and its injection in distilled water leads to some laking of the blood in the same way as the injection of the water alone.[2] It appears to diffuse equally readily into other tissues, and this leads to an interchange of chlorides and urea such as has been described for the bromides and nitrates, for chloride appears in large quantities in the urine.

But this ready diffusion of urea results in its exercising less

[1] It is true that about 0·2 g. of potassium chloride had not been excreted in the urine, but this does not necessarily mean that it was in the blood, for as Magnus found, large quantities of salts disappear into the tissues after injection, and they appear to return to the blood very slowly. The plasma may thus have been deficient in both potassium and sodium at this time.

[2] This is probably the explanation of the very slight diuresis after urea injections noted by some authors, among others by Barcroft and Straub; the disturbance caused by the laking of the blood may also account for the lowered oxygen consumption observed by them after massive intravenous injections of urea.

osmotic pressure against most of the membranes of the body, and urea therefore causes less movement of the fluids than follows the injection of an equivalent amount of sulphate or nitrate. Thus there is much less hydræmia, and there may be no increase in the blood-flow through the kidney, even when large amounts are injected and considerable diuresis is present. In one of Lamy and Mayer's experiments (206) on a dog they made the following observations :—

Time after Injection.	Percentage of Water in Blood.	Blood-flow through Kidneys, per min.	Urea of Blood, per cent.	Urine in 10 mins.	Urea of Urine, per cent.
—	80·1	200 c.c.	0·015	0·6 c.c.	0·7
Intravenous Injection of 30 gr. Urea in 50 c.c. of Water					
1-15 mins.	80	200	0·142	30	2·4
15-30 ,,	75·5	200	0·125	11	3·13
30-60 ,,	83·4	100	0·136	1·1	2·20

The diuresis in this experiment was therefore due to action in the kidney itself, for neither hydræmia nor increased blood-flow were factors when the urine reached its maximum. This purely renal diuresis appears to be due to the difficulty with which urea

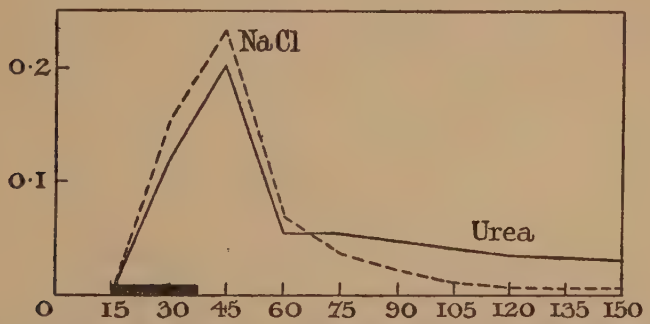

FIG. 32.—The excretion of urea (——) and chloride (- - - -) in the urine of a rabbit which received an injection of a solution containing equal parts of urea and sodium chloride. Time in minutes.

is taken up by the tubules. For as the diuresis passes off, the urea percentage in the urine rises, and the ebb of diuresis has the same gradual fall as is characteristic of sulphate. Thus in an experiment in which a mixture of urea and chloride was injected intravenously (88), the curve of excretion ran as in Fig. 32. The

water and chloride ran together, but the urea fell more slowly than the other constituents in the later part of the curve.

When one ureter is obstructed, and urea and chloride are injected, the urea concentration rises more than the chloride, showing that less of the urea is absorbed when the current is slowed and the conditions are favourable for absorption (see p. 88). Thus in one experiment (1902) I found that at the height of diuresis from the injection of chloride and urea, the urine of the two kidneys presented the following characters :—

	Urine, c.c. in 10 mins.	Chloride.	Urea.
(*a*) Free ureter	22·8	0·1085	0·1121
(*b*) Obstructed ureter . . .	12·3	0·0572	0·08
Percentage $\frac{b}{a}$ . . .	54	53	72

Similarly Yagi and Kuroda lessened the filtration by constricting one renal artery during this diuresis, and found on comparing the urine of the two sides that that secreted by the kidney with constricted artery contained more urea in proportion to the water and salt than the urine of the normal kidney.

	Urine in 10 mins.	Chloride.	Urea.
(*a*) Normal kidney . . .	47·5	0·520	0·369
(*b*) Other kidney . . .	1·9	0·028	0·052
Percentage $\frac{b}{a}$ . . .	4	5	14

The same result was obtained when in a similar experiment the blood-flow through the kidney was diminished by inhibition of the heart. The urine fell in volume and the chloride excretion fell in proportion, but the urea was less changed in total amount and therefore rose in percentage. Increase in the blood supply of the kidney, on the other hand, led to a fall in the percentage of urea, as in that of the sulphates, more water escaping reabsorption in the tubules.

The diuresis induced by urea, so far as it is purely renal in

origin, is due to the urea failing to be absorbed and in its turn preventing the water from being taken up by the epithelium of the tubules. This is well exemplified in the cat in which absorption is extraordinarily efficient. When dry urea is given by the mouth, the urine increases in the next twenty-four hours only by the amount of water which is necessary to carry out the excess of urea in the concentration normal in the cat's urine. The percentage of urea does not rise therefore, but remains constant or may fall slightly.

The diuretic action of urea may thus be purely renal, from the tubules being unable to absorb it. But this is sometimes accompanied by dilution of the blood from increased movement of the fluids of the body, and also by increased blood-flow through the kidney (Henderson and Loewi), and in this case the action in the tubules is reinforced by increased filtration in the capsule. This is much less marked under urea than under most of the salines, however, and urea thus causes less diuresis as a general rule than nitrate or sulphate when injected intravenously in equivalent amounts.

Sugars.

The relation of glucose to the kidney is a specially complicated one, inasmuch as it is reabsorbed by the epithelium when it is present in the filtrate in the normal percentage, but any excess fails to be taken up, and passes into the urine. In this it resembles chloride, but both experimentally and clinically the excess of sugar in the blood over the normal is often much greater than ever occurs in chloride. The excess of sugar in the filtrate over that which can be taken up in the optimal fluid is consequently very large. The unabsorbed sugar in the tubules limits the absorption of water through offering osmotic resistance, and thus excess of sugar in the blood leads to an increase in the urine, whether the sugar is present from disease (diabetes) or is injected intravenously.[1]

The diuresis from the intravenous injection of sugar solutions

[1] The highest possible concentration in the urine is thus of some interest, as it indicates the maximal osmotic pressure against which the tubules can absorb water. In man glucose occurs up to 10 per cent not infrequently, with an osmotic pressure of 9·5 metres of mercury. And higher concentrations are said to have occurred. In the dog the maximal sugar concentration in the urine is said to be 8·5 per cent (389), so that the power of absorption is distinctly lower than in man.

has been the subject of a number of studies, of which those of Lamy and Mayer are the most illuminating. All the soluble sugars are diuretic when injected, but the most efficient are naturally those which are eliminated in the urine in largest amount. Thus lactose and saccharose are more diuretic than glucose, some of which is utilized in the tissues. After a large injection of sugar solution, the blood pressure often rises and the oncometer indicates an increase in the volume of the kidney (Starling, 1899; Albertoni, 1891), but diuresis may occur when both of these are prevented by the injection of chloral along with the sugar (Lamy and Mayer, 1904). Large injections normally increase the blood-flow through the kidney however, and also dilute the blood (Hedon and Arrous). An example may be given from the experiments of Lamy and Mayer (1906), in which they measured the outflow from the vein directly :—

Time after Injection in mins.	Percentage of Water in Blood.	Blood-flow through Kidneys per min.	Urine in 10 mins.
—	78·8	109 c.c.	1·5 c.c.
Injection of 100 c.c. of Water containing 100 grams of Saccharose.			
1-30	79·6	150 c.c.	46 c.c.
30-60	79·3	100 c.c.	43·3 c.c.

In this experiment there is a slight dilution of the blood, but if the concentration of the proteins had been estimated, it is probable that a greater change would have been noted. The blood-flow is much accelerated at first, but the diuresis continued after it had returned to its normal rate, so that little weight can be laid on this as a factor. And when smaller amounts are injected and cause diuresis, the increase in blood-flow and the hydræmia may both be absent. The diuresis in these cases depends on the same factor as in the case of urea, namely, on the excess of sugar failing to be absorbed in the tubules and thus retaining water by its osmotic pressure.

The character of the diuresis also resembles that under urea injection. The urine rises in volume sharply during the injection and falls quickly at first and then tails off slowly. The total concentration, as measured by the depression of the freezing-

point, falls during the rapid diuresis and then increases slowly during the ebb (Galeotti, 1902). But if the urine normally secreted is very low in solids, the sugar injection may increase the concentration even during the diuresis (Lamy and Mayer, 1904). The percentage of sugar in the urine rises continuously, while the chloride falls, especially during the ebb of the diuresis. At this stage therefore the sugar is falling in the blood and rising in concentration in the urine; the chloride is not changing in the blood but is falling in the urine.

The sugar diuresis thus resembles that from urea in most points, and may be accounted for in the same way by the failure of the epithelium to take up the excess of sugar, and its inability to absorb water against the osmotic pressure of the sugar. In sugar diuresis from intravenous injections, however, the accelerated blood-flow through the kidney and the hydræmia probably play a larger rôle than is the case under urea injection. And a further point of difference is the behaviour of the chlorides in the urine. These are excreted in much larger quantity under diuresis from urea than under that from sugar. Apparently the large molecule of sugar has less power of penetrating into the tissues and displacing the salt, or perhaps it causes a larger flow of lymph into the blood. The low percentage of chloride in the diabetic urine is perhaps accentuated by the fact that the patient drinks very large amounts of water and thus superimposes on his high sugar content an excessive secretion of water. The sugar diuresis thus is of the type of those of the sulphate and phosphate.

Remarks on Chapters VIII and IX.

In closing this account of the control of the secretion of the urine by the constituents of the blood—the chemical factors, it may be pointed out that the modern view affords an intelligible account of the means by which this control is exercised. The counterplay of various forces is difficult to follow in detail, and much investigation is still necessary, but most of the chief features may be brought into correlation with known powers, and the discrimination of the kidney is eliminated from the field.

For those who still maintain the view of vital secretion in the kidney, the recent progress in the study of diuresis can scarcely be reassuring, for it reveals a great mass of facts which they can-

not bring into relation. For example, no explanation has been given why in diuresis from any body, such as sulphate or urea, the chloride and phosphate of the urine are augmented, or why the sulphate or urea increases in concentration, as the diuresis passes off, or why in diuresis the urine comes to resemble the plasma in reaction.

The modern view in bringing these observations and many others into some intelligible relation has the advantage, and, in addition, offers a position from which further advance can be made.

CHAPTER X.

THE REACTION OF THE URINE.

ONE of the most important functions of the kidney is the elimination from the body of acid formed in the course of metabolism, for acid is probably the most poisonous of all the waste products known at present. The blood plasma is maintained almost constant in its reaction, at a point slightly more alkaline than distilled water, while the human normal urine is distinctly acid to the ordinary indicators. The change in reaction caused by the kidney is not so marked as is suggested by the statement that the blood is alkaline while the urine is acid. For while litmus indicates such a marked alteration, phenolphthalein remains uncoloured in both blood and urine; in other words, the alkalinity of the blood lies between the limits indicated by litmus and phenolphthalein. On the other hand, the urine is acid to phenolphthalein but alkaline to methyl-orange, so that its acidity is also limited. The work of the kidney consists in shifting the reaction from the limits indicated by phenolphthalein and litmus to those indicated by litmus and methyl-orange. The efficiency of the kidney in eliminating the acids formed in the tissues is very great. Thus Henderson and Palmer calculate that under normal conditions the kidney may free the body of 60-70 c.c. of normal acid per day, while in diabetic coma the amount may be ten times as great.

The reaction of any fluid to indicators depends on the proportion of acid ions (H –) and alkali ions (– HO) contained in it; pure distilled water contains an equal number of these, the concentration of each being less than one in ten million ($0{\cdot}75 \times 10^{-7}$). The addition of hydroxyl ions (e.g. Na – HO) increases the alkalinity, while that of hydrogen ions (e.g. H – Cl) increases the acidity; a neutral salt containing a strong base and a strong acid (e.g. Na – Cl) has no significant effect. But when a salt consisting of a strong ion combined with a weak one is added, the condition changes; by a strong ion is meant one that dissociates readily and has a high velocity, while a weak one tends to remain in combination with some ion of the opposite sign and

moves more slowly. For example, if carbonate of sodium is dissolved in water, the strong Na – ion moves away rapidly from the weak CO_3, which cannot bear to be left alone and thus seeks another partner; it finds one in the H – ions which are present in water, and the two combine and remain in the form – HCO_3. The absorption of – H by the CO_3, however, displaces the equilibrium of water, in which the – H is exactly balanced by – OH, and free OH ions are thus present in excess. The opposite condition is presented when a weak base is present with a strong acid; for example, ferric chloride in solution has an acid reaction (excess of H – ions) because the Fe attaches to itself some of the – OH ions of water, leaving the – H ions unbalanced.

The usual indicators are very weak acids which change colour when they are dissociated. When phenolphthalein is added to distilled water it remains colourless, but when a salt is added, a competition for the cation begins between the phenolphthalein and the added anion; if the anion of the salt is strong, for example – Cl, the indicator is unable to capture any of the cation and the solution remains colourless; but if the anion of the salt is weak (e.g. carbonate), the indicator can supplant some of it and a trace of phenolphthaleinate is formed and this colours the solution. At the same time the hydrolytic dissociation already described occurs, and – HO ions are set free. The indicator thus measures indirectly the proportion of – OH and – H in the solution. The stronger the indicator, the more able is it to compete with the ordinary anions of salts, and thus litmus, which is stronger than phenolphthalein, changes to blue in solutions which leave the latter uncoloured. In the same way methyl-orange is a stronger acid than litmus and therefore changes colour in the presence of salts against the anion of which litmus competes in vain. Solutions may thus be classified according to the indicators which change colour in them, and when this is done, blood is found to lie between litmus and phenolphthalein, while the urine lies between phenolphthalein and methyl-orange.

Another method of measuring the acidity of a fluid is to determine the free – H ions by electrometrical methods, and in this way the acidity may be given in parts per million. The free – H ions in distilled water amount to 0·75 in ten million, and these are balanced by an equal number of – HO ions. In the blood the – H ions are 0·4 in ten million ($0{\cdot}4 \times 10^{-7}$), and they are no longer equal to the – OH ions which amount to 7·2 in ten million ($7{\cdot}2 \times 10^{-7}$). In the normal human urine, Henderson and Palmer found the – H ion concentration vary from 160 to 0·4 in ten million (160×10^{-7} to $0{\cdot}4 \times 10^{-7}$). These two methods of estimating acidity give exactly similar results.

The acidity of the urine may be compared with that of phosphoric acid to which sodium hydrate is slowly added. It is found that the highest acidity observed in the urine corresponds to the point at which enough hydrate has been added to change almost the whole of the acid into acid sodium phosphate. The lowest acidity corresponds to a solution of Na_2HPO_4 diluted to 0·01 normal (Henderson and Palmer). The reaction of the

urine thus lies almost exactly between that of NaH_2PO_4 and that of Na_2HPO_4.

This "acidity" or "hydrogen ion concentration" (C_{H+}) is quite distinct from the "total acidity," which is measured by titration with alkali.[1] This is evident from the consideration that the "acidity" is the same whatever the quantity of urine examined, while of course the titrable acid increases with the amount of urine taken. The – H ion measures the intensity of the reaction, the titration merely the amount of the acid present; the distinction is the same as that between the pressure of steam and the total amount of steam in a boiler. A certain relation exists between them; in the urine the "acidity" proper varies in larger limits than the total acid per cent, but it rises and falls along with it (Henderson and Palmer, 1914). This is of course to be expected. For if alkali is added to urine, the first effect is to neutralize the most readily dissociated – H ions, while those with more ties to their anions remain unsaturated; but the – H ion concentration only denotes the most active ion, and if it be estimated as titration proceeds, it is found to diminish gradually as the less dissociated combinations alone remain.

The limits of the hydrogen ion concentration in the urine preclude the possibility of more than a trace of any of the stronger acids being present, and indicate clearly that the acidity is due to a weakly dissociated acid. As has been stated, they correspond almost exactly to the range between NaH_2PO_4 and Na_2HPO_4; and the dissociation of the second hydrogen of phosphoric acid is only slight and corresponds exactly to the theoretical requirements. The total acidity of the urine is found to be limited by the amount of phosphate present; the phosphate is naturally found in much larger quantity than the titrable acid, for some of it is present as neutral phosphate, but the acidity is never greater than can be accounted for by the phosphate.[2]

When the concentration of – H ions is high, some of the weak organic acids are also dissociated. Thus Henderson and

[1] Useful accounts of this distinction are given by Rhorer (1901) and Höber (1903).

[2] This has been disputed by Dreser (1905), who estimated the intensity of the acidity by an indirect method, which seems liable to considerable experimental error not counterbalanced by any clear advantage.

Palmer (1913) state that the hippuric acid may be dissociated to the extent of 8 per cent, aceto-acetic acid and lactic acid to 11-12 per cent, oxybutyric acid to 45 per cent, and uric acid to 91 per cent. But the main factor in the acidity is the varying amount of secondary phosphate present. The importance of the phosphates in determining the reaction of the urine was shown in my experiments on diuresis in the dog (1904). For example a dog received an injection of 400 c.c. dextrose solution (10 per cent), and the urine collected from the right ureter was titrated against phenolphthalein with decinormal potash. After the diuresis had begun to pass off, an injection of sodium chloride and sodium phosphate was given and the urine was titrated in the same way. During the glucose diuresis the urine required from 2·5-10 c.c. of decinormal potash to neutralize 100 c.c. to phenolphthalein, while during the diuresis from phosphate 50-60 c.c. of potash was required for each 100 of urine; and this in spite of the fact that the phosphate was slightly alkaline. The same fact was shown by Trevan in experiments in which the frog's kidney was perfused with Ringer's solution; the urine had exactly the same reaction as the Ringer, but when a neutral mixture of phosphate was added to the perfusing fluid, the urine became acid.

The function of the kidney in preserving the normal reaction of the blood is to eliminate the acid while retaining as far as possible the alkali; its powers in this direction are limited, for it cannot separate a strong acid from the base with which it is combined in the blood, as the gastric glands do. It is therefore confined to changing the almost neutral mixture of phosphates of the blood to the distinctly acid mixture in the urine; in other words, it changes the proportions of Na_2HPO_4 and NaH_2PO_4 in favour of NaH_2PO_4, thus retaining a certain amount of – Na and – HO in the body.

$$Na_2HPO_4 + H_2O \rightleftarrows Na - HO + NaH_2PO_4.$$

The Na – HO of course does not leave the kidney cell as the actual hydrate, but as the hydrolysed carbonate.

A general consensus of opinion exists that this change occurs in the renal tubules, and not in the glomerulus, for all agree that the glomerular fluid is practically neutral in reaction like the blood plasma. But here agreement ceases, for the followers of Bowman and Heidenhain hold that the tubular epithelium, taking

up neutral phosphate from the blood, throws it in a more acid form into the tubules and returns the alkali to the blood again; the modern theory, on the other hand, states that the glomerular filtrate corresponds to the plasma in its phosphate content, and that the epithelium absorbs the sodium and hydroxyl ions in the form of bicarbonate, while the phosphate ion is rejected by it and passes into the ureter enriched in hydrogen. The one school asserts that acid is actively excreted, the other that alkali is actively absorbed.

In favour of the secretion of acid several sets of experiments on the frog are cited. In the first of these, Dreser (1885) injected acid fuchsin into the lymph sacs of frogs and found it excreted in the urine. Histological examination of the kidney showed that it was present in the lumen of the tubules, but the cells remained unstained. After some hours, however, the granular staining of the cells of the convoluted tubules was seen, as has been recently described by Suzuki for carmine (p. 63). In these respects it therefore resembled the other stains; but Dreser points out that this dye is coloured only in acid, and therefore concludes that the granules which were stained by it were in an acid medium, or, as he puts it, that the stain was excreted by the cells along with acid. The presence of the dye in the tubules before the cells showed any colour suggests that the dye was mainly eliminated through the capsule (see p. 63), but the vital staining of the granules with the acid fuchsin certainly indicates that the reaction in their interior is acid, if the granules were really coloured during life. The possibility that the fuchsin was stored in colourless form in the granules *intra vitam* and only became coloured as the acid diffused into the cells from the tubules after death, has not been excluded, however. In other experiments, the renal arteries in the frog were ligatured, and acid fuchsin injected into the renal-portal vein elicited the typical red coloration of the convoluted tubules; but no urine was secreted, and it is not clear whether any of the dye was actually seen in the lumen or whether it was confined to the granules of the cells, so that this experiment is not decisive.

Bainbridge and Beddard ligatured the renal artery in the frog, and found that when urea and phosphate were injected together, the urine was more acid than when urea alone was injected. They conclude that the tubules alone can secrete urine more acid than

the blood, perhaps even more acid than the normal urine (see discussion on p. 78).

Trevan states that when the renal artery of the frog is perfused with Ringer's solution, the urine is of the same reaction as the Ringer, but if neutral phosphate is now run into the renal-portal system, the urine becomes distinctly more acid than either perfusing fluid; he concludes that the Ringer's fluid passes through the capsule and acid phosphate is added to it as it passes through the tubules. And this experiment would prove conclusively that the acid is secreted by the tubules, if it could be clearly shown that the glomerulus is really supplied only with Ringer's fluid. But the frog's kidney is a very small object, and there is no question that fluids diffuse through it rapidly. The possibility cannot be excluded that the phosphate, circulating through the renal-portal vein and theoretically reaching only the cells of the tubules, may also diffuse into the lymph spaces and reach the capsule in this indirect way.

On the other hand, there is no reason to suppose that the phosphates differ from other salts in their behaviour in the kidney. They elicit diuresis, and in other respects resemble the sulphates very closely. And these results in the frog are not sufficiently unequivocal to determine the view that the phosphates do not pass through the capsule. It has been shown already (p. 154) that the phosphate ion, once it has reached the tubule, is not absorbed but escapes into the ureter, like the sulphate ion or urea. It enters the tubule associated with sodium ions which are themselves capable of absorption, unless they are retained by their being combined with a non-permeating anion; for example, the sodium ions of Na_2SO_4 cannot desert the sulphate and thus reach the blood. The special hydrolysis of the phosphates creates a different condition, which may be represented by the following figure of the di-sodium phosphate as it leaves the glomerular capsule:—

$$\begin{matrix} H- \\ -OH \end{matrix} + \begin{matrix} Na- \\ =HPO_4 \end{matrix} \quad \begin{matrix} Na- \\ \end{matrix} \rightleftarrows \boxed{\begin{matrix} Na \\ OH \end{matrix}} + \begin{matrix} -Na-H \\ HPO_4 \end{matrix}$$

Here the permeating sodium may associate itself with another absorbable ion (– OH), leaving the phosphate poorer in sodium but richer in hydrogen. Or another exchange may occur between the phosphate and the carbonate, since the HCO_3 ion is absorbed readily by the tubules (90):—

$$\begin{matrix} -\mathrm{Na}-\mathrm{Na} \\ \mathrm{HPO_4} \end{matrix} + \begin{matrix} \mathrm{Na}- \\ \mathrm{HCO_3} \end{matrix} \rightleftarrows \begin{matrix} \mathrm{Na}-\mathrm{H}- \\ -\mathrm{HPO_4} \end{matrix} + \boxed{\begin{matrix} \mathrm{Na} \\ \mathrm{NaCO_3} \end{matrix}}$$

I have enclosed within dotted lines the molecule undergoing absorption in the tubules, the rest of the right half of the equation remaining in the urine. This process of absorption requires a certain amount of time, and if the glomerular fluid is very abundant, the elaboration of acid urine may be imperfect; in diuresis the reaction is therefore less acid and approaches that of the plasma more or less closely (Rüdel and many others). This change in reaction in diuresis is further developed by the relative poverty of phosphate in the plasma and therefore in the capsular fluid. For in diuresis induced by phosphate or by a mixture of salts containing phosphates, the urine does not tend to approach the neutral point so much as in ordinary diuresis from sulphates or chlorides without phosphates (see p. 168). But even in well-marked phosphate diuresis, the flood of glomerular filtrate cannot be sufficiently elaborated by the tubules, and the acidity is low. As the diuresis passes off and the tubules can cope better with it, the acidity may become very marked.

If diuresis is induced by phosphate and the flow through the tubules is restricted by partial obstruction of one ureter, so that the tubules have to deal with a smaller amount of filtrate and that at greater leisure, the acidity increases to a marked extent on that side and the percentage phosphate rises in accordance with it. For example, in an experiment in which phosphate solution was injected intravenously in a dog in which one kidney had to work against a pressure of 25 mm. Hg in the ureter, I found (1904) the following titrable acidity of the urine in the two ureters. The acidity is expressed in c.c. of decinormal potash required to neutralize to phenolphthalein and litmus respectively :—

	Total Urine.	Acidity (Phenolphthalein).		Acidity (Litmus).		P_2O_5.	
		Actual.	Per Cent.	Actual.	Per Cent.	Actual.	Per Cent.
Free ureter .	79	12·6	16	4·7	6	0·162	0·205
Obstructed ureter	34·5	9·5	27·4	5·2	15	0·135	0·390

Very often the urine on the obstructed side gave a distinct red to litmus, while that on the free side gave a violet neutral shade, so that not only the titrable acid was greater when the flow of urine was slower, but the actual concentration of hydrogen ions was greater on that side. In other words, the elaboration of the glomerular fluid in the tubules changes the proportion of phosphate and sodium to the disadvantage of the latter. And as has been stated previously, the effect of obstruction of the ureter is to promote absorption in the tubules of absorbable substances, of which the sodium ion is one.

The urine may be made alkaline to litmus by giving alkalies, which of course reach the kidney in the form of carbonates and bicarbonates. The alkalinity is limited, however, never going beyond that of the blood, and never giving the alkaline reaction with phenolphthalein. The urine never reaches beyond the stage of Na_2HPO_4, therefore, in its reaction, no normal sodium phosphate can exist in it. The limited alkalinity of the urine is due to the presence of anions which can compete with the weak phenolphthalein anion, though they are overcome by the stronger litmus. These are the $-CO_3$ ions, which escape from the capsule like the other plasma ions. They differ from the phosphates in being absorbed by the tubules, for in diuresis from carbonate, obstruction of the ureter leads to a marked fall in the carbonate of the urine, both actual and in percentage. The carbonate ion in fact is as readily taken up by the epithelium as water, chloride, or glucose. And in all probability the sodium derived from the phosphate escapes from the tubule in combination with carbonate for the most part. In an experiment in which one ureter was obstructed and diuresis was induced by the injection of a mixture of phosphate and carbonate of sodium, I obtained the following proportions on the two sides:—

	Urine.	Acidity (Phenolphthalein).		P_2O_5 mg.	CO_2 mg.	Cl mg.
		Actual.	Per Cent.			
Free ureter (*a*) .	53·7	13·5	25	304	56	46·2
Obstructed ureter (*b*)	16·6	10·1	61	166	2	4·4
$\frac{b}{a}$ per cent . .	31	75		56	4	10

The carbonate percentage thus decreased, while the acidity and phosphate rose. If the plasma contains excess of sodium carbonate and bicarbonate, however, it is eliminated in the same way as excess of chloride or sugar. In the blood the alkalinity is restricted by the presence of CO_2 in the tissues, and the same limit is placed on the reaction of the urine. The urine of herbivora contains a large percentage of carbonate derived from the salts of organic acids consumed in the food; these acids are oxidized in part in the tissues to bicarbonates, which are eliminated in the urine in the same way as other bodies present in excess in the plasma. Herbivora fed on proteins, however, develop an acid urine, resembling that of man and the carnivora.

To sum up the modern view of the reaction of the urine: The essential factors are (1) the presence of salts in the glomerular filtrate, which are extensively hydrolysed and of which the cations can be absorbed while the anion is rejected by the tubular epithelium, and (2) adequate absorption in the tubules. The phosphates alone fulfil these conditions completely. The carbonates fail to do so because the anion is absorbed.

CHAPTER XI.

THE ACTION OF DIURETICS AND OTHER DRUGS.

Caffeine group — digitalis — pituitary — adrenaline — mercury — atropine and pilocarpine—calcium.

THE most efficient diuretics are the three xanthine compounds, caffeine, theobromine[1] and theophylline, the action of which on the kidney was first examined by v. Schroeder, and which have formed a subject of investigation ever since. This diuresis is best seen in the rabbit and man, is very slight in the dog, and is not induced in the cat. Even in the rabbit the xanthine compounds often fail to increase the urine if the animal has been supplied with food containing little water, and the diuresis is small in man in the normal condition compared with the profuse flow which is often seen where there is an accumulation of fluid (dropsy, anasarca) in the tissues. In normal dogs no definite diuresis follows the ingestion of caffeine, but when hydræmia and diuresis are caused by a constant infusion of saline, these bodies increase the diuresis to a marked extent (Loeb). Some diuresis follows the ingestion of theobromine (Anten) and theophylline in the normal dog, but it is less marked than that in man.

Schroeder attributed the diuresis to direct action on the kidney, as he could not find any evidence that the fluid in the general tissues is changed by caffeine, except in so far as is obviously the result of the loss of water and salts through the kidney; and this has been almost universally accepted since.[2] The blood naturally becomes more concentrated from a large amount of water being withdrawn from it (Schroeder, Loewi, Fletcher and Henderson).

[1] Theobromine is very insoluble and is only slowly absorbed, so that it is generally used in the form of a double salt, sodium-theobromine, salicylate (diuretine).

[2] Comparatively recently it has been suggested by Marfori and Chistoni that in addition to its direct renal action, caffeine may affect the fluid exchange by changes in the lymph production, but this has been negatived by Gaisböck.

The diuresis is accompanied by an augmented excretion of the solids of the urine (Fig. 33), though these do not rise in the same proportion as the fluid (Schroeder), so that the specific gravity of the urine falls under caffeine, and its molecular concentration is lower, as is shown in experiments in which the depression of the freezing-point of the urine is measured (Widmer, Dreser, 1904).

Among the solids of the urine, the chloride excretion has been examined by many investigators, who agree that the total chloride excreted in a unit of time is increased by caffeine and its

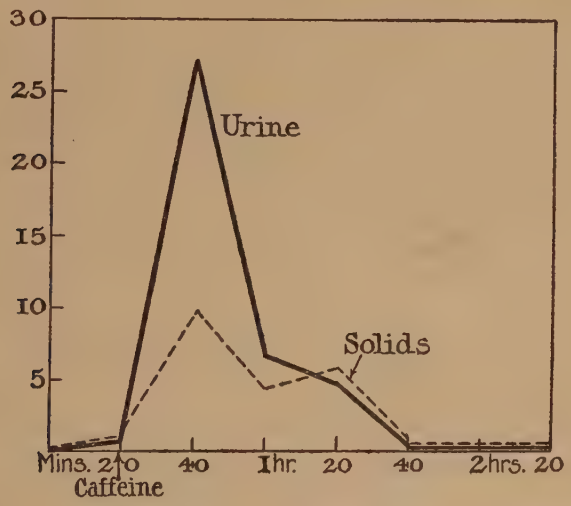

FIG. 33.—The excretion of water (——) and of solids (- - -) in the urine of the rabbit under caffeine. (After v. Schroeder's protocols.)

allies. If the rabbit has been fed on a diet rich in salts and has accordingly been passing urine with a high percentage of chloride, the latter is lower during the diuresis, while if the diet has been deficient in chloride and the urine has previously contained little of this anion, the percentage may rise during the diuresis (Frey, 128). An extreme example of this is given by Grünwald, who fed rabbits on maize until the chlorides disappeared from the urine altogether, but they reappeared during diuresis from theobromine. But in these salt-poor animals, even at the height of the diuresis, the total excretion per minute is always lower than in caffeine diuresis in animals in a normal state of nutrition (Widmer). The change in the proportion of water and chloride during diuresis

thus depends on the conditions of the urine previously; in every case the urine under caffeine diuresis approaches the serum in respect of its chloride percentage, the latter falling if the urine was rich, and rising if it was poor in chloride previously. In animals in which part of the chloride of the blood is replaced by bromide, the excretion of bromide under caffeine is exactly analogous to that of the chloride (Frey, 1910-11).

The distribution of sodium and potassium in the urine has been examined by Katsuyama, but only in the twenty-four hours' urine, which does not give a sufficiently accurate picture of the changes during a diuresis which may only last one to two hours. Bock (1911), estimating them in hourly periods, found both sodium and potassium increased in total amount during the diuresis, while the percentage of each was lower than before it began; the general course of the excretion during the diuresis was similar to that of the chloride; the sodium rose more than the potassium (Fig. 34). If the urine is alkaline, as in normal rabbits, caffeine reduces the alkalinity, while, on the other hand, in starved rabbits, in which the urine is acid, the reaction tends to become slightly alkaline under caffeine; in each case the urine approaches the plasma in reaction. Of the other constituents of the urine, the urea increases in absolute amount and falls in percentage (Schroeder, Anten), and the phosphate also increases (Bock); but the change in these is less than that of the sodium and chloride. When glycosuria is present, the sugar rises in amount under diuresis (Loeb). The caffeine group often induces glycosuria in the rabbit (Jacobj, 1895), but this does not arise from

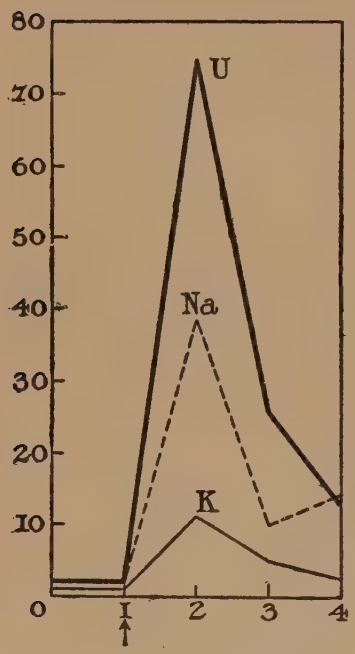

FIG. 34. — The fluid, sodium, and potassium of the urine of the rabbit under theophylline given as indicated by the arrow. Time in hours. (After an experiment by Bock.)

action on the kidney, but from the presence of excess of sugar in the blood (literature given by Nishi, 1909, and Stenstrom). In birds caffeine induces marked diuresis, during which the uric acid is not much altered in absolute amount and falls considerably in percentage (Sharpe).

The effects of caffeine and its allies on the circulation have been investigated repeatedly. Schroeder, who first analysed the diuretic action, was quite clear that the diuresis is independent of these, and later work has only confirmed his position. The intravenous injection of caffeine is often followed by a trifling rise in the general blood pressure, but sometimes the first effect is a short fall from action on the heart (Philipps and Bradford). The rise was ascribed to stimulation of the vaso-constrictor centre (Schroeder), and the consequent constriction of the renal vessels was said to retard the onset of diuresis. Under chloral and caffeine this rise is absent, and the diuresis is more marked. Phillips and Bradford, in oncometer experiments, found the renal volume fall at first from a direct action on the walls of the renal vessels, and the secretion fell or stopped altogether, but the volume soon rose far above the normal, and a rapid flow of urine began. Successive injections caused the same fall in volume, and the subsequent rise became less and less marked, and finally was no longer elicited, and diuresis likewise ceased. Later investigators have all confirmed Philipps and Bradford's statement that caffeine diuresis is generally accompanied by a rise in the oncometer lever (Starling, Gottlieb and Magnus (140), Loewi, Fletcher and Henderson). This has generally been regarded as evidence that the renal vessels are dilated during caffeine diuresis, but the fallacy of this conclusion has already been pointed out. And in some instances diuresis occurs without any change in the oncometer volume, while very often the curve of secretion and of volume show marked divergences.[1]

[1] Loewi, Fletcher and Henderson imbedded the kidney in gypsum to prevent any increase in volume, and still found diuresis occur under caffeine, but the blood in the renal vein assumed the arterial colour, which they interpret as an indication of vascular dilatation. But this method seems exceptionally liable to error of observation from the bias of the observer, and Magnus (1909, p. 510) was unable to confirm the observation. Asher and Michaud found that theophylline diuresis is interrupted if blood is drawn from an artery, but this cannot be regarded as bearing on the question, since in the one experiment in which they measured the blood pressure, it fell about one-third during the hæmorrhage, and this is enough to interfere with any form of diuresis.

In rabbits supplied with dry fodder, or, in which the kidney has been injured previously by anæmia, no secretion may occur from caffeine, although the oncometer shows an increase in the volume of the kidney (229, 17); and similarly, repeated injections may fail to cause diuresis before its action in increasing the volume disappears. Loewi and his associates hold that the primary action of caffeine as a diuretic is dilatation of the renal vessels, which in favourable conditions causes diuresis. But this neglects the repeated observations in which the diuresis diverged from the oncometer volume.

Unfortunately, direct measurements of the blood supply of the kidney are not many, and are generally unsatisfactory. Landergren and Tigerstedt found the blood-flow in the kidney accelerated, but their method precluded diuresis. Munk and others found the kidney vessels dilated when they were perfused with caffeine, but no increase in the urine occurred. Schwarz (1899) observed some diuresis in a rabbit with no change in the outflow from the renal vein, but the blood-flow is very small in this experiment. In Barcroft and Straub's experiments there was no diuresis, and the same is true of Robertson's work on dogs. The only definite statement is the recent one by Richards and Plant, who found that in the kidney kept alive by a special form of perfusion, caffeine may cause diuresis, though no change in the blood-flow through the kidney is possible.

Allard has examined the effects of raising the pressure in the ureter by obstructing it partially in a case of *ectopia vesicae* in man; unfortunately the theophylline was preceded by a large amount of water, salt, or urea, which obscures the picture of the diuresis. He found that the effects of resistance in the ureter under theophylline were closely similar to those under salines and water. This agrees with the earlier results with theobromine of Filehne and Ruschhaupt on rabbits, in which the urine was reduced in amount without any very significant change in composition, and the only inference that can be drawn is that the absorption in the tubules is not altered by the action of these purine bodies. Frey states (1906, p. 175) that the maximal ureter pressure shows little increase during caffeine action, but his experiments appear to have been performed on dogs in which caffeine causes little diuresis.

Section of the renal nerves increases the diuretic action of

caffeine (Schroeder) by increasing the blood-flow through the kidney, but otherwise the diuresis is independent of the nervous system.

The oxygen consumption by the kidney during purine diuresis has not been satisfactorily determined, for though Barcroft and Straub found some increase in two experiments in which caffeine was injected, in neither was there any significant diuresis. After large repeated doses the oxygen consumption of the resting kidney was abnormally low; the injection of sodium chloride continued to cause diuresis.

The action of caffeine in the frog's kidney has been examined by Cullis (1906)[1] who infused a 0·1 per cent solution of caffeine-sodium benzoate through the renal-portal system (see p. 79), the glomerulus being still supplied by the heart and thus receiving a mixture of blood, saline, and caffeine. A considerable diuresis began at once, and continued after the heart was excised and the kidney received only the caffeine solution by the renal-portal vein; and the urine contained chloride, sulphate, and dextrose if these were present in the perfused liquid or if they had been supplied in it previously to the caffeine. The rate of flow through the kidney was accelerated by caffeine dilating the vessels. No certain results were obtained when caffeine was perfused through the artery alone, and Cullis infers from her experiments that caffeine stimulates the tubule cells to secretion in small doses, while it paralyses them in 0·5 per cent concentration. But the fact that no certain results were obtained when caffeine was perfused through the artery, casts a doubt on this conclusion, for here both glomerulus and tubule were exposed to its action; in venous perfusion the only difference as regards the epithelium of the tubules is that the pressure in the capillaries was probably higher. In addition to some defects in the method already mentioned (p. 80), it may be remarked that the concentration of caffeine used was far too great; in fact, 0·1 per cent of caffeine was used by Bainbridge (1913) in order to poison the kidney, and the strength used by Cullis is sufficient to cause rigor in muscles exposed to it.

Rowntree and Geraghty mention that caffeine perfused through the renal-portal system alone causes diuresis, but do not state the concentration employed. Barcroft (33) states that the oxygen consumption is increased in the frog's kidney by caffeine perfused through the renal-portal vein, but gives no details of the experiment, and it is rendered equivocal by the fact that sulphate which causes no secretion also increases the O_2 consumption. I do not think that any inference can be drawn from these experiments in regard to the action of caffeine in the frog. And Barcroft and Straub's view that caffeine first stimulates and in large doses paralyses the activity of the renal tubules appears to rest upon experiments in which there was no diuresis whatever, and may be disregarded.

[1] Halsey also examined the action of theobromine in frogs with ligatured renal artery, but apparently did not determine whether the glomerular circulation was entirely suppressed, so that his results are inconclusive.

Sobieranski (1895) observed that during caffeine diuresis the epithelium of the tubules is less stained by indigotate than in normal animals, and draws the inference that caffeine causes diuresis by paralysing the absorption by the cells of the tubules; but he observed the same effect from caffeine in dogs, in which there was no diuresis, and this is sufficient to negative his conclusion; Heidenhain had stated long before that the tubules were only stained when the secretion of urine was restricted or altogether prevented. Modrakowski records some observations on the histological appearances of the renal tubules under caffeine, and Hjelt describes a change in the arrangement of the granules in the contorted tubules; the granules in the outer part of the cell are displaced by numerous threads of homogeneous appearance, while the inner part of the cell is filled with numerous small granules.

The action of the purine diuretics has been attributed by Schroeder and other believers in vital secretion, to stimulation of the renal cells to higher activity. This must presumably extend to the epithelium of the glomerulus as well as to that of the tubules, for all the constituents of the urine are augmented although not in equal ratio; some apparently hold (Barcroft and Straub) that the stimulation is limited to the cells of the tubules.

Among the holders of the secretion-reabsorption view, Sobieranski suggested, on grounds which have already received attention, that caffeine and its allies cause diuresis by lessening the absorption in the tubules. But this would not explain the whole, for constituents such as phosphates and urea which are not returned to the blood by the normal kidney are increased in quantity during the diuresis.

This consideration suggests that the caffeine diuresis is glomerular in origin. And Loewi holds that it is due to increased filtration from the capillaries, arising from caffeine dilating the renal arterioles by a specific action on their walls. The objection may be raised that diuresis may occur without dilatation, or even when, as in his own experiments, special precautions are taken to prevent any increase in the volume of the kidney. And that the kidney should contain more blood in its vessels and more fluid in its tubules and yet show no increase in its volume, seems inexplicable. The question requires further examination by methods in which the blood-flow during adequate diuresis is measured independently of the volume of the kidney.

If the diuresis from caffeine proves not to depend on the vascular changes, it will indicate that the alkaloid acts on the

glomerular capsule, in all probability by reducing the resistance to filtration. This would increase the amount of the filtrate without changing the relative proportions of its constituents, but these of course would undergo some elaboration in their passage along the tubules. No such alteration in the capsule has hitherto been shown to occur, but the hypothesis is frequently made to explain phenomena observed in other cells, and a change in the rate of filtration through a membrane is known to occur in chemical manipulations. The secondary phase, in which caffeine fails to cause diuresis after repeated administration, may arise from a further change in the capsule.

The Digitalis Series.

Digitalis was introduced into therapeutics by Withering as a diuretic, and squills, which resembles it in action, has been used for this purpose for many centuries. Their specific action on the heart was a more recent discovery. It is generally recognized that the glucosides of this series have little or no direct action on the kidney, and that the increase in the urine, which so often follows their use, is the result of the changes in the heart and circulation. Some doubt is expressed as to whether the improved efficiency of the heart, or an altered distribution of the blood, contributes more to the augmentation of the blood supply in the kidney, which is the immediate cause of the diuresis. For while the augmented efficiency is generally acknowledged to be a factor, Gottlieb (1912) holds that therapeutic doses of these remedies cause some narrowing of the arteries of the intestine, and that the blood current is thus diverted from the bowel to the kidney, the vessels of which are not constricted and may even be dilated by these doses. Into this dispute it is fortunately unnecessary to enter here; suffice it to say that while there is no question of the cardiac factor in the digitalis diuresis, the vascular factor has not been established with the same certainty.

The changes in the renal volume under digitalis have been frequently examined by means of the oncometer, and here again it is agreed that large quantities lessen the volume of the kidney, while the blood pressure is much increased. Under smaller doses Loewi and Jonescu found the volume increased and the urine augmented in quantity. They conclude that the renal vessels

are dilated during digitalis diuresis, but this inference is not permissible, for, as has been pointed out previously, the increase in volume may arise from the fluid accumulating in the tubules, and not from any change in the calibre of the vessels. Philipps and Bradford found that in dogs large doses of digitalis cause a distinct fall in the oncometer tracing often accompanied by some increase in the urine, while Brunton and Power found large doses of digitalis rather lessen than increase the urine in dogs, and Marshall had the same experience in rabbits. Pfaff, on the other hand, observed distinct diuresis in rabbits from the injection of digitalis. The difference in the results of these observers probably arises from the use of different quantities of the drug, and from the food of the animals previous to its administration. Rabbits are known to react to purine diuretics only when they have received abundant watery food previously, and the same is probably true of digitalis. It is clear that a small dose may accelerate the blood-flow through the kidney by improving the heart, and perhaps by diverting the blood to the kidney, while a larger one may constrict the renal vessels and thus actually lessen the flow through them. And Brunton and Power state that the diuresis does not accompany the very high blood pressure which is observed under large doses of digitalis, but only sets in when this has begun to fall.

In man, digitalis hardly increases the urine in health, while in cardiac dropsy it may cause a profuse flow, especially in cases of auricular fibrillation. Whether dropsy from other cardiac conditions responds as satisfactorily, is not definitely known. In promoting the circulation in the tissues in general, digitalis probably induces the reabsorption of fluid from the cavities, and this return of fluid to the blood would in turn cause diuresis, so that in these cases the diuresis may be in part due to the accelerated circulation in the kidney itself, in part to the increased fluid of the blood. The quickened circulation in the kidney acts in part mechanically, in part, doubtless, by improving its nutrition. The changes in the solid constituents of the urine under digitalis resemble those under other forms of diuresis caused by changes in the rate of the blood-flow through the kidney. Thus Steyrer (1902) found that the total chloride was increased and even the percentage rose slightly ; the total nitrogen was augmented to a less extent (Fig. 35).

The diuresis of digitalis treatment is still imperfectly investigated; even less is known as to the diuresis under squills, while of strophanthus it can only be said that there is a general belief that it is less efficient as a diuretic than digitalis or squills; even this limited statement is not satisfactorily established.

Pituitary Extract.

The extract of the posterior lobe of the pituitary body was shown by Schäfer and his associates to increase the secretion of the kidney when it was injected intravenously. This diuresis is accompanied by a considerable increase in the volume of the kidney and by increased general blood pressure from constriction

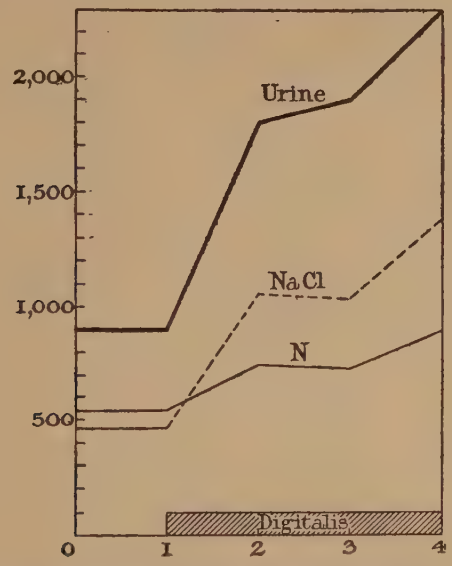

FIG. 35.—The rise in the secretion of urine, chloride, and total nitrogen in a case of cardiac dropsy treated with digitalis. Time in days. (After Steyrer's protocols.)

of the vessels in other organs. Schäfer holds that the diuresis is not wholly vascular in origin, but arises from some direct action on the kidney cells, though this direct action is no doubt greatly assisted by the renal vasodilatation and rise of blood pressure. And he points out that diuresis may occur under the extract without any change in the blood pressure or increase of the renal volume, especially when a second injection is given. Houghton

and Merrill, perhaps impressed by the general similarity in the behaviour of the kidney under small doses of digitalis, have regarded the diuresis as entirely secondary to the changes in the circulation. The change in the vessels of the kidney has been determined only by the oncometer,[1] and the difficulties of interpreting its tracing during diuresis have been mentioned repeatedly. But there seems every reason to believe that the vessels undergo dilatation under the extract, and in the presence of this factor it is very difficult to determine whether there is also any direct action on the kidney itself. The subject must be investigated by other methods of determining the blood supply to the kidney. It is probable that the same active principle induces the changes in the circulation and in the kidney, whether these are independent or not (Dale).

Adrenaline.

Adrenaline injected intravenously constricts the renal vessels and lessens or arrests the secretion of the urine. Given by subcutaneous injection, it increases the sugar of the blood and often causes glycosuria. Marshall and Davis state that in cats the extirpation of the suprarenal bodies leads to marked impairment of the kidney activity, which is signalized by the urea of the blood rising to twice its normal concentration.

Mercury.

The value of mercury in various forms in increasing the secretion of the urine has been recognized in clinical medicine for centuries, and a good deal of work has been done in the last few years to elucidate its action. Like other diuretics, calomel has a much greater effect when there is an accumulation of fluid in the tissues than in normal conditions, and clinically it is most useful in the dropsy of cardiac inefficiency. The total chlorides and nitrogen of the urine rise while the percentage falls (Steyrer, 1902), (Fig. 36). The diuresis resembles in its known features that caused by a considerable group of irritant substances such as aloin, chromates, uranium, and cantharidin, which all, like mercury, increase the urine in small doses, and cause nephritis

[1] Except in Robertson's estimation of the flow from the vein, which did not give any definite increase in the blood supply.

in larger quantities (see Chapter on Nephritis); and cantharidin has sometimes been employed as a diuretic. It is therefore natural to suppose that the diuresis arises from a direct action on the kidney, perhaps from a mild irritation which may increase the filtration in the glomerulus and at the same time dilate the vessels.

Many investigators believe, however, that the diuresis from mercury does not arise from a direct renal action, but from changes in the other tissues,

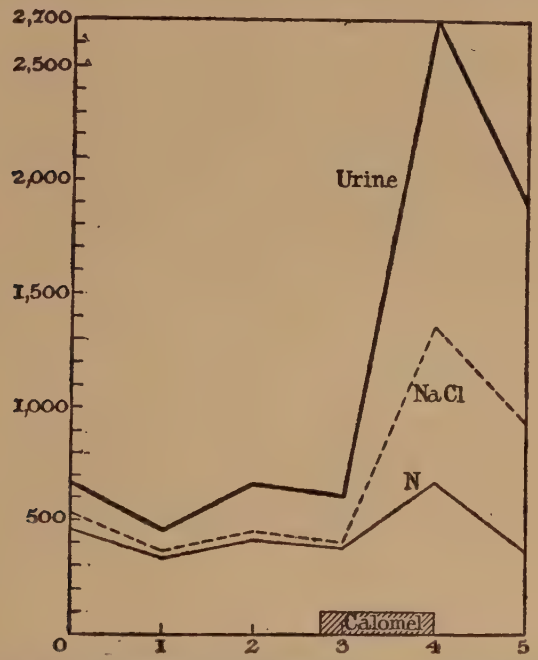

FIG. 36.—The effect of calomel on the secretion of the urine, chloride, and total nitrogen in a case of cardiac dropsy. Time in days. (After Steyrer's protocols.)

while others hold that both factors are present. Thus Jendrassik states that the blood becomes more dilute during calomel diuresis, and that this indicates that the reabsorption from the serous cavities is the real cause of the diuresis. Cohnstein observed diuresis in rabbits from the hypodermic or intravenous injection of calomel, but his experiments are invalidated by his dissolving it in sodium thiosulphate, which has diuretic properties itself; his conclusion that the mercury diuresis is due to action on the circulation is thus not established. A similar objection may be made to Frey's experiments (127) in which calomel was given by the stomach along with considerable amounts of water. Fleckseder found hydræmia in rabbits during the mercury diuresis, and ascribes this and the diuresis to the reabsorption of fluid from the large

bowel, which does not seem a satisfactory theory. Vejux-Tyrode and Nelson found that mercury varies greatly in its diuretic action in animals, and this agrees with clinical experience.

Many other drugs have some popular reputation as diuretics, but are of little importance, and their method of action has not been investigated. Some increase the urine only by the amount of water which is administered along with them.

Atropine and Pilocarpine.

The characteristic action of these alkaloids on the true glands is not developed in the kidney. Some writers state that the urine is often reduced in amount by atropine and increased by pilocarpine (Thompson (1894), Walti), but the change is often slight or absent altogether (Eichelberg). And Loewi (1903) is probably correct in attributing the rather inconstant effects of these alkaloids on the secretion of the urine to the changes in the circulation rather than to any direct action on the kidney. Cow (1912), the most recent writer on the question, points out that the effects on the other secretions and on the ureters may also alter the secretion of urine after atropine.

In this respect again the kidney differs from most true secretory glands, although some of these, notably the mammary, also fail to react to atropine and pilocarpine.

Calcium.

In the curious craze for the use of lime salts, which played such a large part in therapeutics a few years ago, their action on the kidney was also invoked. MacCallum (1904) announced that the diuresis from saline injection could be arrested by calcium chloride, but this was shown by Lamy and Mayer (208) to be due to the general action on the circulation of the doses he employed. They found that moderate quantities of calcium injected intravenously increase the urine like sodium chloride, and this is confirmed by Porges and Pribram and Bonnamour and Imbert. Lime salts have also been advocated in nephritis in the hope that they would lessen the albuminuria and exercise a sedative action on the inflamed cells. Eisner states, however, that his cases showed no improvement under this treatment, and not

infrequently became worse, as was shown by the symptoms and also by the rate of excretion of various of the test substances employed to determine the excretory activity. In the healthy kidney he could not find any deleterious action from calcium salts taken by the mouth.

CHAPTER XII.

GLYCOSURIA.

Phlorhizin Glycosuria.

PHLORHIZIN was found by v. Mering to cause marked glycosuria in animals when it was administered to them by the mouth or subcutaneously. And as no increase in the sugar of the blood could be made out, he came to the conclusion that the glycosuria from phlorhizin is the result of changes in the kidney, which is aroused to secrete sugar; the changes in the general metabolism under phlorhizin are the result of the loss of sugar, not the cause of the glycosuria, as in true diabetes. This view, that the kidney action is the primary one, has been contested repeatedly,[1] but has always been reconfirmed (Erlandsen), and may be considered to be universally held now. Apart from the evidence that the sugar of the blood is not appreciably increased by phlorhizin, but is often lowered by it, an experiment of Zuntz is often cited in support of the renal origin of the glycosuria. He put a cannula into each ureter of a dog and then injected phlorhizin into the renal artery on one side. Sugar appeared in the urine dropping from the ureter on that side in a few minutes, and only later in that from the other side. This experiment has been confirmed by Lepine and by Pavy, Brodie, and Siau, and seems to show definitely that the glycosuria is due to changes in the kidney. As the blood sugar is drained off by the kidney, it is constantly renewed by the tissues, and in this way phlorhizin induces changes in the general metabolism, which present analogies in many respects with those observed in true diabetes, in which the metabolic changes are the primary feature and the glycosuria only a secondary result.

The sugar in the urine under phlorhizin varies in amount with

[1] The literature is given by Lusk.

the dose and other circumstances. Its concentration also varies from 3 per cent or lower up to 10 or even 15 per cent; the concentration in the urine may therefore be about 100 times as great as that in the blood plasma. The amount of urine is increased, but the diuresis under phlorhizin is comparatively slight; the characteristic feature is not the amount of urine, but the glucose it contains.

Of the other constituents of the urine, the chlorides are very little altered in absolute amount in the dog according to Loewi (227 and 230), while Biberfeld (49) states that they may be reduced, though this appears to be exceptional from his experiments, and Lepine and Maltet state that they may actually rise in percentage and therefore in total amount. It may be gathered from these discrepancies that no significant change occurs in the total amount of chloride, and that such small variations as have been observed depend on differences in the amount of the diuresis or in the excretion of chloride previous to the injection of phlorhizin. The percentage of chloride almost invariably falls during the glycosuria. In the rabbit, I found some increase in the total amount and sometimes in the percentage of chloride under phlorhizin, and this agrees with Ruschhaupt (320).

The urea, the total nitrogen and the phosphates show no definite change during the acute phlorhizin glycosuria, but if the treatment is prolonged, so that the general metabolism is seriously altered, it results in increased nitrogen output and the other symptoms of carbohydrate starvation; this of course is only an indirect effect of the renal action and need not be discussed here. During the acute phase, the total molecular concentration of the urine may be reduced in spite of the presence of sugar in quantity (Frey, 1906, p. 204), but others have found a very high specific gravity. The primary effect of phlorhizin is therefore to cause glycosuria with a moderate increase in the fluid of the urine and no significant change in the other components.

A difference of opinion has been expressed as to the effect of further diuresis superimposed on an existing phlorhizin glycosuria, Weber holding that the total sugar excreted is increased, while Knopf and Loewi and Neubauer (1908) deny that any change occurs in it; their experiments suggest, however, that some increase in the sugar occurs, though much smaller than that in the fluid.

Spiro and Vogt observed that when glycosuria was elicited in dogs by the continued intravenous injection of glucose, phloridzin causes a distinct rise in the concentration of sugar in the urine, which is somewhat reduced in quantity ; the same sudden fall in the amount of urine is caused by a phlorhizin injection in the course of diuresis from sodium chloride. They state that when cane sugar is injected intravenously and is being excreted in the urine, the injection of phlorhizin augments the cane sugar secretion and no glucose appears in the urine. As no details of their experiments have been published, it is impossible to discuss their results, which are surprising. Lepine and Maltet state that the elimination of rosaniline-trisulphonate is not increased by phlorhizin.

In the kidneys of dogs treated with phlorhizin for some days, Trambusti and Nesti found that the epithelium of the convoluted tubules had undergone extensive coagulation necrosis, and in some tubules was entirely absent, and Policard and Garnier state that this sets in very rapidly after the injection of phlorhizin. The glomerulus showed no abnormal appearance. Kossa states that in rabbits the injection is almost always followed by cloudy swelling of the cells of the tubules and albuminuria, while Coolen found no albuminuria induced in dogs. It may be questioned whether these changes are the direct effects of the phlorhizin, as renal degeneration is liable to occur from the alteration of the metabolism ; and no mention is made of albumin in the urine or of pathological changes in the kidney by other investigators.

The distribution of the sugar in the kidney under phlorhizin has been examined by Seelig, who placed small pieces in phenylhydrazine and found phenylglucosazone crystals distributed chiefly in the interstitial tissues between the tubules. These were sparely present in the capsule and absent in the lumen of the tubules. Nishi (1910) estimated quantitatively the amount of sugar in the medulla and cortex of the kidneys of rabbits under phlorhizin, and found that while in normal animals the medulla contains no sugar, it now had a higher percentage than the cortex ; this may only indicate that urine containing a high percentage of sugar was present in the tubules, whereas a comparatively small proportion was contained in the blood and capsule of the cortex.

The glycosuria and diuresis from phlorhizin appear to be independent of mechanical changes in the circulation of the kidney. For though a slight fall in the blood pressure is occasionally observed and the volume of the kidney shows a corresponding shrinkage, this is transient and appears to arise from impairment of the heart's action through too rapid injection. Apart from this, the volume of the kidney shows no change, and in particular the oncometer suggests no increase in the blood-flow

(Pavy, Brodie and Siau). Schwarz (1899) found that in his defibrinated dogs, the glycosuria from phlorhizin was not accompanied by any acceleration of the blood-flow, and this was confirmed by more satisfactory methods by Barcroft and Brodie (1905-6). The glycosuria occurs after section of the renal nerves. The maximal ureter pressure may be slightly higher during the glycosuria (Frey, 1906, p. 204).

A large increase in the oxygen consumption of the kidney was found by Barcroft and Brodie to occur during glycosuria from phlorhizin. Schwarz (1902) found that when the outflow from the ureter was obstructed on one side and the quantity of urine on that side rose (see p. 13), the amount of sugar on that side also increased absolutely and per cent under phlorhizin. And this is confirmed by Brodie and Cullis. On the other hand, Allard in his experiments on man with partial obstruction of the ureter, found that after phlorhizin the urine on the obstructed side was less in amount, and contained a lower percentage of chloride, while the sugar was increased in percentage, though the total amount was smaller than on the normal one. Thus the sugar resembles urea in behaviour.

Bainbridge and Beddard state that in frogs in which the glomerular blood supply is abolished by ligature of the renal artery (see p. 75), phlorhizin injected into the lymph sac along with urea causes the secretion of urine containing a reducing body, while urea alone is followed by apparently normal urine.[1] And Cullis on perfusing Ringer's solution containing 0·1 per cent of phlorhizin through the renal-portal vein of the frog, observed diuresis and glycosuria; the addition of dextrose increased the action of phlorhizin to a remarkable extent. The objections to these experiments on the frog have been discussed already (p. 83), and here it need only be remarked that Bainbridge and Beddard found that 0·1 gram of phlorhizin injected into the lymph sac injured the kidney tubules, and that this must have been caused by the concentration used by Cullis; further, as the fluid perfused by Cullis contained no reducing body, the reduction observed from the urine after phlorhizin must have arisen from

[1] Mosberg states that phlorhizin causes glycosuria in these frogs, but his experiments are not quite convincing, as he failed to ascertain that the glomerular circulation was completely suppressed.

something contained in the renal cells or from the phlorhizin itself.

Nephritis induced by chromate, aloin, or cantharidin prevents the glycosuria of phloridzin (Schabad, Richter (1900), Weber), if the lesion is sufficiently severe. Hellin and Spiro diverge from these other writers in regard to chromate and aloin, perhaps because in their experiments the kidney was less injured; the tubules show the most obvious injury under these poisons, but the capsule is also impaired. Baer and Blum found that the phloridzin glycosuria is prevented by a whole series of organic dibasic acids, and this has been shown by Underhill in the case of one of these, tartaric acid, to be due to nephritis induced by it; probably the same explanation holds for the other bodies of the series.[1]

The glycosuria from phlorhizin has been attributed to the drug exciting the epithelial cells of the tubules to the secretion of sugar, and the slight increase in the urine has been supposed to be due to the water secreted along with the sugar. The chief positive evidence in favour of this appears to be the experiments on the frog with ligatured renal arteries or under perfusion, and needs no further discussion, as its equivocal nature has been pointed out (p. 83). An *a priori* objection to this view of secretion of sugar by the renal tubules lies in the fact that according to Heidenhain the glycosuria from the presence of sugar in excess in the blood arises from the glomerulus; even Loewi, and Pavy and his collaborators, who believe that phlorhizin arouses the tubules to the secretion of sugar, hold this view of the other forms of glycosuria. The action of phlorhizin, then, is regarded not as a lowering of the limit at which the kidney reacts to the sugar of the blood, but as the imposition of a new function on a set of cells which have not the power of secreting sugar normally; and this is contrary to all experience in the action of drugs and poisons, which are only capable of raising or lowering the normal function of a cell. Unless absolute proof to the contrary is forthcoming, the secretion of sugar under phlorhizin must be attributed to the same structure as the secretion in hyperglycæmia. Phlorhizin would thus be regarded as merely lowering the threshold at

[1] Ringer (1912) has criticised Baer and Blum's statement in regard to glutaric acid, and apparently with justice.

which a pre-existing function comes into action, not as creating a new one.

Some evidence against the view that the glucose under phlorhizin is secreted by the tubules and in favour of its origin in the capsule is offered by my experiments (1917). In these, a cat received an injection of phlorhizin, and after glycosuria had set in, one kidney was excised and the blood pressure was reduced by section of the cord until no further secretion of urine occurred. After an hour the second kidney was excised, and the content of sugar in each was estimated. If the phlorhizin caused the secretion of glucose by the tubules, the second kidney would presumably have contained more sugar, for the epithelium would have continued to secrete it into the tubules, and it could not escape into the ureter as no urine was secreted. But no increase in the sugar content occurred in the second kidney. The secretion of sugar by the kidney thus ceased at the same time as the secretion of urine, and this suggests that water and sugar are shed out by the same apparatus—the glomerular capsule.

A special view, which was suggested as a bare possibility by Minkowski (252), and which has perhaps received more attention than its author ever expected or designed, is that phlorhizin acts as a vehicle for the carriage of sugar through the renal cell. Phlorhizin is itself a glucoside compounded of glucose and phloretin, and the latter also causes glycosuria in the same way as phlorhizin, although to a less extent. It was suggested that phlorhizin gives up its glucose and the phloretin again combines with glucose from the blood, and this alternate synthesis and decomposition plays some part in the glycosuria. There is, however, no evidence whatever that phloretin can combine to phlorhizin in the tissues, and small quantities of the glucoside are sufficient to cause marked glycosuria, so that it is necessary to assume that the discharge and recharge of the phloretin with glucose must occur with extraordinary rapidity. And this "vehicle" view affords no assistance to understanding the passage of sugar through the kidney, for it is just as difficult to conceive that phlorhizin passes to and fro as that sugar passes through.

Another curious view has been put forward by Pavy, Brodie, and Siau, that the cells of the renal tubule actually form sugar from some constituent of the blood; Loewi had the same idea in a more definite form, that the sugar is liberated by the cells from the colloid combination in which it circulates; neither view is confirmed by later observers, who have shown that when the sugar is prevented from escaping in the urine, phlorhizin does not increase the free sugar of the blood.

The modern view is that in the normal kidney sugar is filtered through the capsule and is reabsorbed in the tubules as long as

the proportion in the plasma and in the glomerular filtrate does not exceed the normal limits.[1] But the sugar can only be absorbed by the tubules along with the appropriate amount of water, chloride, etc., and when more sugar occurs in the filtrate (in hyperglycæmia) than is required to form this dilute absorbable fluid, the excess of sugar appears in the urine along with the urea and other waste products. This unabsorbed sugar retains a certain amount of water by osmotic resistance and the urine is thus increased. Under phlorhizin, the filtration is unchanged, but the absorption of sugar is diminished or arrested by a specific action in the tubules, while that of chloride and water remains unaffected, except through the osmotic pressure of the unabsorbed sugar, which retains some water. The phlorhizin thus reduces the threshold at which sugar is rejected by the cells of the tubules. It may be objected that the failure of one constituent of a solution to be absorbed while others pass through readily, makes a large draft upon credibility, but it may be pointed out that phlorhizin only extends to glucose the normal behaviour of the renal cell towards urea, and in physics analogies are presented in the behaviour of semi-permeable membranes to different salts. And the absorption in the tubules depends on an unknown process, which may very well be modified by the presence of phlorhizin. The chief difficulties in this view are presented by the action in the frog observed by Bainbridge and Beddard, but as has been pointed out, these experiments, while excluding the blood circulation in the glomerulus, by no means exclude that of the lymph. Another difficulty is presented by experiments in which diuresis is superimposed on an existing phlorhizin glycosuria; for if the amount of filtrate is increased, while its sugar percentage remains unchanged, and none of the sugar is reabsorbed in the tubules, the total sugar of the urine must of course be augmented.[2] This is stated to be the case by Weber,

[1] Biberfeld (1907) has suggested that under normal conditions the sugar of the blood is not excreted because the kidney cell utilizes it for its own nutrition; under phlorhizin the combustion of sugar is arrested in the renal cell and the sugar is thus allowed to escape. It has also been suggested that sugar escapes in the glomerular filtrate, but is taken up and utilized by the cells of the tubules, and thus never returns to the blood. This might perhaps be worked out by accurate investigations of the "respiratory quotient" of the kidney.

[2] This actually occurs when diuresis is superimposed on the glycosuria of pancreatic diabetes, and also in glycosuria in the rabbit from the administration of sugar (Loewi, 1902).

while Loewi's experiments seem to be opposed to it. In order to substantiate this objection, it would be necessary to show that the glucose concentration of the plasma is unchanged during the diuresis, and this has not been done; in fact, variations in the amount of glucose in the plasma may well be the explanation of the divergent results of Weber and Loewi, for the former used theophylline as a diuretic, the latter sodium chloride.

An interesting parallel to the effect of phlorhizin on the glucose excretion is offered in that of phenylquinoline carbonic acid (atophan) and related bodies on the elimination of uric acid. For it seems clear from Folin and Lyman's observations that atophan changes the behaviour of the kidney to uric acid, which is allowed to escape in larger quantities than normally. Now uric acid is one of the threshold substances like glucose, although they differ in the limit at which they are maintained in the blood. If, as has been assumed in the modern view, these threshold bodies are reabsorbed in the tubules, atophan must restrict the reabsorption of urate, just as phlorhizin restricts the reabsorption of sugar. No other constituent of the urine is changed in amount by the action of atophan, which is as specific for urate as phlorhizin is for glucose.

Other Forms of Glycosuria.

In most other forms of glycosuria, there is excess of sugar in the blood, and the kidney simply excretes it in the way which has been discussed under sugar diuresis.

In the diuresis caused by the intravenous injection of large quantities of saline solution in the rabbit, Bock and Hoffmann found sugar in the urine, and this has been confirmed repeatedly. Here there is no excess of sugar in the blood, but a distinctly lower concentration (384, 385); the percentage of sugar in the urine is always very low. This glycosuria is generally regarded as secondary to the diuresis; in the modern view the rush of fluid through the tubules prevents the reabsorption of sugar which normally occurs. The believers in specific secretion also ascribe this form of glycosuria to the kidney being flooded and thus unable to elaborate its secretion, and herein apparently abandon the view of specific secretion in the kidney; for, on their view, the capsule is not permeable by sugar and therefore does not secrete

it, and it is quite inexplicable how the presence of excess of permeable substances, chloride and water, should change the permeability of the capsule towards sugar.

Other saline solutions, such as nitrate and acetate of sodium, also cause glycosuria in the rabbit when injected in dilute solution in large quantities (Külz). The saline glycosuria is often arrested by the injection of lime salts, but it is unknown whether this arises from the constrictor action of calcium on the vessels, or from some more obscure relation.

It has also been shown that some metallic poisons, mercury, chromium and uranium, and less often cantharidin, cause glycosuria not infrequently, without any increase in the sugar of the blood. It is true that some writers describe a hyperglycæmia under these poisons, but there can be little doubt that this is not invariably present (Pollak, Frank, Konschegg). The sugar in the urine under these poisons is always small in quantity and in low concentration (0·5-1·0 per cent), and it is not by any means constant in its appearance (Richter); Frank states that glycosuria is more frequent in mild cases of poisoning, and that it often precedes the albuminuria which occurs under these drugs. He points out that they act more especially on the convoluted tubules, where the sugar is excreted in diabetes according to his view, and suggests that these poisons lower the threshold of activity in these cells, so that even when the blood contains only its normal content of sugar they react to it as if it were in excess. An equally facile account of the phenomenon would refer it to these cells being impaired in function by the poisons, and thus being unable to absorb the sugar of the glomerular filtrate completely. Further investigation is required before any satisfactory conclusions can be drawn in regard to this condition.

As regards the glycosuria from the presence of sugar in excess in the blood, little need be added to what has been said under sugar diuresis. It has been pointed out of recent years that the kidney varies in its response to hyperglycæmia. Thus in the rabbit even if the sugar content of the blood is normal, glycosuria occurs if diuresis is marked, and as the glycæmia increases, less diuresis is required to cause glycosuria, until when the blood contains more than 0·25 per cent of sugar, the urine also contains it without any significant increase in fluid (Pollak). On the other hand, there is some evidence that the permeability

of the renal cells by sugar may change; thus in diabetes in man there is often considerable excess of sugar in the blood without it appearing in the urine, especially when the kidney has undergone cirrhotic changes, and, according to Pollak, repeated injection of adrenaline changes the kidney in the same way, at any rate as regards some causes of glycosuria, though uranium continues to act as usual. Similarly glycosuria may be arrested reflexly by irritation of the peritoneum and other sensory excitation. This is probably due to restriction of the arterial supply to the kidney, which diminishes the glomerular filtrate and allows it to be more completely elaborated in the tubules.

CHAPTER XIII.

PERFUSION OF THE KIDNEY.

THE factors that influence the secretion of the kidney are so many and their interaction so complex, that attempts have frequently been made to eliminate at any rate the external influences by artificial perfusion of the excised kidney. The most notable of these form the subject of several papers by Munk (1887-8), and by Jacobj (1890-91), but less extensive researches have been made by many others (see Pfaff and Vejux-Tyrode). As far as concerns the secretion of the urine, these older investigations are of no definite value, and these papers are only of historical interest, for the technique was altogether wanting in many respects in which later research has shown that the utmost attention is imperatively demanded. Thus in the light of Pfaff and Tyrode's results, the blood used for perfusion must not be defibrinated; it is probable that hirudinized blood does not injure the kidney. And the renal circulation must not be interrupted for the introduction of cannulæ into the artery and vein, for it has been demonstrated beyond discussion that anæmia lasting for only a minute is sufficient to arrest the renal secretion for nearly an hour. The blood supplied to the kidney must be adequate, at least 2-3 c.c. per gram per minute.

In all of these essential points, the older perfusions were lacking; and it is therefore surprising to find Munk's results still cited as evidence for or against different views of renal activity. It is true that in the absence of any precautions and with or without the use of the various complicated apparatus designed to replace the heart and lungs, a fluid exudes from the ureter of the perfused kidney; but it has few of the characters of urine. The first few drops are obviously not the result of the secretion under perfusion, but consist of the urine remaining in the collect-

ing tubules. And after these have been passed, the fluid from the ureter appears to be merely an exudation, which contains more or less protein and often hæmoglobin, is slightly alkaline in reaction, and contains salts and other constituents in practically the proportion in which they occur in the perfused fluid. These experiments have not succeeded so far as to maintain a flow of liquid with the characters of urine for even a few minutes. It is possible that the more elaborate mechanisms devised by Jacobj, Brodie, or Richards and Drinker, along with improved technique, may succeed in keeping the epithelial cells alive, in the same way as simpler methods maintain the unstriated muscle of the renal vessels and of other muscular organs in a condition simulating the normal, but until recently this has not been done.

The fluid obtained from the ureter in ordinary perfusion is an exudate formed by filtration through the renal cells, probably largely through the capsule. But it differs from the glomerular filtrate of the living kidney in containing protein; the capsule is therefore changed in character, and no deductions can be made from the constitution of the exudate as to that of the normal filtrate.

Quite recently, perfusions have been carried out by Bainbridge and Evans and by Richards and Plant, in which the kidney was almost completely isolated and was supplied in the first instance from the heart of another animal, in the second, by a mechanical pump. The blood was prevented from clotting by hirudin and was adequate in amount. There was no interruption of the renal circulation, for the artificial supply was carried to the kidney through cannulæ inserted in the aorta below the renal artery, and the perfusion began before the natural channel from the heart was interrupted. These very difficult experiments seem to have been entirely successful in maintaining the normal activity of the kidney, and a further extension of the method promises to yield important results.

The kidney has been perfused with saline solution for many purposes, chiefly to determine changes in the calibre of the vessels. A large number of these experiments have been done by Sollmann (1905, 1907) with the object of determining how far the mechanical and physical factors obtaining in the dead kidney can be used to explain some of the phenomena of the living organ. Fluid is readily obtained from the ureter by

this method, but again it is merely a filtrate from the perfused fluid and possesses none of the characters of urine. Many other investigators have perfused the kidney in researches on the reactions of the vessels, and some in the hope of obtaining a secretion of urine. Even if the difficulties already discussed can be overcome, it seems unlikely that Ringer's solution can convey enough oxygen to supply the needs of the kidney, assuming that it suffices for other purposes.

The observations of Guthrie (1910) are hardly encouraging; he compared the effects on the kidney of simply occluding the artery for a definite time with those obtained when the artery was closed and the kidney was washed out with various saline solutions; the perfused kidney was distinctly more injured than the simply occluded one, as was shown by its failure to recover completely when the circulation was restored.

Demoor has tried to investigate the processes occurring in the kidney by contrasting the effects of perfusion with hypotonic (0·6-0·7 per cent) with those of hypertonic (1·1-1·2 per cent.) salt solutions. He concludes that fluid is drawn from the cells of the organ by hypertonic solutions circulated through the vessels, while hypotonic solutions may withdraw fluid from the tubules after reaching them; as he gives no details, it is impossible to estimate what grounds may exist for these conclusions.

CHAPTER XIV.

ALBUMINURIA.

THE normal kidney is practically impermeable by the plasma proteins, though a trace of serum albumen is said by Mörner to be constantly present in the urine. The presence of protein in quantity in the urine is the commonest symptom of disturbance of the kidney.

But while the plasma proteins are retained by the kidney, some other proteins reaching the blood stream are eliminated by it. Thus egg albumen injected intravenously, or even when swallowed in large quantities by some people, reappears in the urine (Lehmann, Ponfick). Hæmoglobin freed in the blood also escapes through the kidney fairly quickly. Caseinogen is also said to be eliminated in this way when it is injected intravenously, and gelatin passes out slowly. The other proteins hitherto examined fail to pass out by the kidney.

The evidence is fairly conclusive that these proteins pass through the capsule; for masses of egg-white and hæmoglobin may be detected in its interior when the kidney is excised and hardened during the secretion (Posner, Adami, Ribbert, 1894 and 1913). Thus Ribbert showed that when laked blood is injected into a rabbit's ear vein and the kidney is excised after five minutes and hardened, the hæmoglobin is present only in the capsule, while if the animal is allowed to survive ten minutes, hæmoglobin is still present in the capsule, but has also extended into the tubules.[1]

[1] Miller (1912) states that hæmoglobin may be detected by special stains in the epithelial cells of the convoluted tubules and the loop of Henle, but Baehr (1913) points out that this may be of the same nature as the granular staining with special stains (see p. 62), and thus accepts Ribbert's view that the hæmoglobin issues from the capsule and is concentrated in its passage through the tubules by the absorption of the fluid. Suzuki suggests that hæmoglobin may escape also through the tubules, which show signs of injury when the excretion is very marked, but this is purely conjectural to account for some occasional appearances, which may arise from the

Adams found that when the blood pressure was reduced by section of the spinal cord and no urine was secreted therefore, egg albumen was also absent from the capsule and tubules. Adami, repeating this with hæmoglobin, found it appear in the capsule, but the quantity of fluid injected by him was probably sufficient to reinstate the capsular filtration. Adami showed that the excretion of hæmoglobin is accelerated by nitrate, and Schmid confirms this for the excretion of egg albumen, which is accelerated by saline or caffeine diuresis. Nussbaum found that temporary ligature of the renal artery in the frog leads to albuminuria after release of the ligature, and concludes that injury of the capsule alone without the tubules being involved is sufficient to cause albuminuria.

The concentration of hæmoglobin in the urine is often higher than that free in the plasma, and this suggested to Adami that the protein is concentrated in the capsule and not filtered, but this concentration undoubtedly occurs from the absorption of fluid in the passage of the filtrate along the tubules (Suzuki, Baehr, Ribbert).

The actual amount of egg albumen excreted by the kidney varies greatly. Thus in one of Schmid's experiments only about one-fifteenth of that injected was excreted in one and a half hours; in others the proportion seems higher. Lehmann and Stokvis noted that in some instances more albumen appeared within twenty-four hours than had been injected, and concluded that the albumen of the urine after the injection of egg-white must be derived in part from the body proteins. This was shown to be correct by Ascoli by means of an antigen reaction, though most of the protein in the urine is the injected egg-white (Inouye). The passage of egg-white through the kidney must therefore injure the cells so that they are no longer impermeable by the blood proteins. It is unknown whether this holds also for hæmoglobin, but it seems probable (Schmidt, 1907); the injury is only transient. In the only case which has been investigated, therefore, the excretion of injected protein seems to occur only with injury to the capsule, so that it still remains true that the

pigment diffusing into the edges of the cells from the lumen. The elimination by the capsule has been proved, that by the convoluted tubules is merely suggested on the grounds which have been mentioned under carmine (p. 64). The literature is discussed by Lehnert (1912).

normal capsule is not permeated by proteins. Hamburger found that on repeated injections of egg-white, the albuminuria decreases and finally disappears, the renal cells having become immune to the foreign protein; this is further evidence that this form of albuminuria arises from changes in the capsule, and that the egg-white acts on it not merely as a foreign body to be excreted, but also as a toxin.

The albuminuria described by Pfaff and Vejux-Tyrode as occurring from the intravenous injection of the animal's own defibrinated blood (see p. 118), may be of the same nature as that caused by egg-white or hæmoglobin, the changes in the proteins from defibrination sufficing to render them poisonous to the capsule.

Albuminuria can readily be induced experimentally by interrupting the blood supply of the kidney by compression of the artery or vein, or of the ureter, which leads to pressure on the vein. When the renal artery is clamped for ten to thirty seconds, the secretion of urine ceases completely, and is reinstated only slowly after an hour or more; the urine contains abundant protein at first, and gives the ordinary tests for it for many hours, then the percentage of albumin falls slowly, and ultimately the urine resumes its ordinary character.

This form of albuminuria is unquestionably due to the permeability of the capsule being altered by asphyxia so that it permits the passage of the proteins of the blood. For Posner and Seelig found on hardening the kidney excised during the albuminuria that the capsule contained granular masses of protein; Seelig attempts to draw a distinction between this form and that due to venous compression, in which he found the protein in the tubules, but the difference is probably accidental, the protein in the tubules really originating from the capsule (Telemann). In another series of experiments, Seelig induced albuminuria by compression of the thorax in rabbits, and here at one stage he found the protein almost confined to the capsule, while in animals which had survived longer it extended into the tubules also. The compression of the thorax apparently affects the kidney by disturbing its blood supply.

Albuminuria occurs in man very frequently from heart disease, which decreases the blood supply to the kidney and thus induces partial asphyxia. It has been much discussed whether this is

due to the rise in venous pressure from stagnation in the great veins or to diminished arterial flow, but both factors may probably be involved, and in any case the effect on the kidney is the same; the capsule becomes altered and allows the passage of plasma protein.

In acute and chronic parenchymatous nephritis in man, albuminuria is a prominent symptom, and here also the protein is derived from the glomerulus, for Posner found the capsule distended with a granular solid in human kidneys hardened by heat, and others have confirmed his statement. The protein passes down the tubules in which it may also be detected in the same way. Generally the albuminous fluid from the capsule is enriched in its passage through the tubules by the detritus of the degenerating cells, or by whole cells or cell-masses stripped off the basement membrane. Very often the protein solution is solidified in the tubules, by the absorption of the water together with the increasing acidity, and a "cast" of the tubule is formed and is finally driven downwards by the pressure from behind and appears in the urine. The appearance of these casts varies according to the point at which the protein solidifies and the condition of the tubules through which they pass. The chief constituent is generally the protein derived from the capsule, but the most prominent features may be lent by the detritus and more or less degenerated cells from the tubules. It has not been established that the tubules add anything to the albuminous glomerular fluid except the remains of the degenerated epithelial cells, but it is not unlikely that lymph may exude from the denuded surface as it does from other unprotected cells.

Albumin in the urine thus originates from the capsule (Runeberg), though it may receive accretions from the tubules. When much albumin is present, the urine is diminished in amount, and all its constituents are reduced in approximately the same ratio (Soetbeer). This seems to point to one of two conditions; the altered capsule continues to allow the ordinary constituents to pass through, but in diminished quantity, or some of the capsules and tubules escape and continue to secrete as usual, while the affected ones cease altogether to form urine and simply allow lymph to exude from the surface. The albumin would then be supplied by some units of the kidney and the urine by others. It seems likely that in most cases the diseased capsule and tubules

continue their function of forming urine even though the amount is reduced; for it is difficult to suppose that all the units are not equally affected when the renal artery is closed temporarily. Yet a typical albuminuria with diminished urine containing the ordinary constituents results. It is probable, therefore, that the change in the capsule which admits of the passage of the blood proteins, at the same time retards the passage of the ordinary filtrate. Possibly the slow passage of the big protein molecule obstructs the current through the capsule; a similar effect is often seen in the filtration of colloid fluids in the laboratory.

Not infrequently, however, this diminution in the filtrate has a further effect, in that the "no-threshold" substances, such as urea, are eliminated in larger proportions than the "threshold" chloride and water (Widal and Javal). The scanty urine then contains a high percentage of urea and often of protein, while the chloride is unusually low. Œdema appears and is increased by the administration of chloride, while it is lessened by a salt-poor diet, or by the administration of urea or of caffeine diuretics. It may be suggested that the slow transit through the tubules may permit very complete reabsorption. The addition of salt to the diet makes up the water to the optimal solution, and it is thus more readily absorbed than if it passed through the capsule with less chloride; on the other hand, urea prevents its absorption in the tubules, and caffeine, by increasing the flow through the capsule, opposes the condition of slowed filtration.

The amount of protein in the urine varies with the acuteness and severity of the nephritis; Gross found from 0·17 to 4·5 per cent in different patients. Under diuresis the percentage of protein may remain unchanged or may fall (Emerson, Sollmann and McComb).

Cloetta states that the relative proportion of the proteins in the urine is different from that in the blood, the albumin being present in higher ratio than the globulin. Several observers hold that this protein quotient is of value in prognosis, the larger the quotient $\frac{\text{albumin}}{\text{globulin}}$, the less severe the lesion and the better the prospect of recovery (Hoffmann). There may, however, be some doubt whether in a complex fluid like the urine, the proteins can be separated satisfactorily by the ordinary salt precipitation, and Gross, in an elaborate analysis of the urine proteins in nephritis

in man and rabbits, failed to corroborate Cloetta's statement. According to him, the urine contains albumin, euglobulin, and pseudoglobulin in varying proportions, which bear no relation to the total protein in the urine or to the severity of the disease. Moreover, the globulins are present in the urine in larger quantities than those given by Cloetta, and not infrequently exceed the albumin, so that the quotient becomes less than unity. Its importance is thus in dispute.

Albumin occurs in the urine from the administration of a large number of poisons, but most attention has been given to that following the administration of cantharidin, mercury, chromates, and vanadates. These are often divided into two groups, of which cantharidin is said to act on the glomerulus and capsule chiefly, while mercury, chromates, and vanadates are credited with a specific action on the convoluted tubules. There is doubtless some difference in their action, but there is no question that it is often exaggerated. For all of them cause albuminuria and therefore act on the capsule, and in the case of chromates Posner has shown the typical granular precipitate in the capsule. And on the other hand, cantharidin like the others induces inflammation and degeneration of the epithelium of the convoluted tubules, though this is often less marked in the beginning than that caused by the second group. The difference is thus not absolute but merely in degree, and perhaps has received more attention than it merits (see pp. 212-216).

Excretion of Bacteria by the Kidney.

It is now a familiar clinical fact that in infections bacteria may pass from the blood into the urine and that they may be grown in cultures inoculated from the urine. In experiments in which cultures of various germs were injected intravenously in animals, the urine was found to contain them in a few minutes. There is every reason to believe that they pass through the normal uninjured kidney, and that, on the other hand, the vitality of the germ is unchanged except from its exposure to the acid urine. On histological examination they are found in the capillary loops of the glomerulus and in the interior of the capsule (Klecki) and in the lumen of the tubules, but rarely in the cells lining them. The way of escape is thus through the capsule almost or quite

exclusively. Biedl and Kraus thought that their appearance in the urine was accelerated by diuresis; but Klecki could find no change from diuresis from caffeine, sugar, or large infusions of salt solution. It has been suggested that the bacteria pass through the capsule by active movements, but this has been shown to be unnecessary, for minute granules of dead matter are also found in the urine after they have been injected intravenously.

CHAPTER XV.

NOTES ON NEPHRITIS AND OTHER RENAL DISORDERS.

In nephritis the chief changes in the urine are two in number—albuminuria and casts, and a diminution in the amount of all the constituents of the urine. In chronic cirrhosis, however, the urine may be in excess and very little albumin may be secreted, but in this form of disease the nephritis is accompanied by changes in the general circulation which mask the effects of the local disease of the kidney, and it may therefore be dismissed from consideration at present.

The more acute the attack, the greater the concentration of albumin and the smaller the secretion of urine, and this may culminate in the passage of blood or in complete anuria. The albuminuria points to affection of the glomerulus (see chapter xiv.), and the oliguria also suggests this, at any rate to those who regard filtration as the chief factor in the urine formation. But the histological examination of the kidney very often detects no abnormality in the glomerulus and capsule, while the tubules present every sign of disorganization and degeneration of the cells. The attention of pathologists has therefore been directed almost wholly to the alteration in the epithelial cells of the tubules, and those experimental investigators who have of late years begun to look into the function of the diseased kidney, have been too much dominated by these morphological considerations. It cannot be overlooked, however, that the only definite evidence during life that the tubules are involved in the disease is the appearance of granular and epithelial casts with more or less detritus of the cells of the tubules. That the glomerulus is the place of origin of the albumin may be taken as established (see p. 201).

It must be added that many pathologists have held that the primary factor in nephritis is the lesion in the glomerulus.

Among the most eminent supporters of this view,[1] Ribbert and Senator may be mentioned. The glomerulus and the capsule generally present no abnormal post-mortem appearances in nephritis, it is true, but this must not be accepted as evidence that the capsule is not involved in the lesion. Everything points to the capsule being an extremely delicate structure which deteriorates under comparatively slight injuries; thus a short interruption of its blood supply is enough to change its character so that it no longer is impermeable to proteins, and its permeability by the non-protein constituents and water is lessened. And it must not be forgotten that the microscope has only been used to examine the dead and hardened capsule and that we are still unacquainted with the appearance of the living membrane. The absence of obvious differences between the dead nephritic capsule and the dead normal one does not exclude the possibility of marked differences between them during life. But however this may be in regard to morphological changes, there can be no question as to the differences in function between the normal and the nephritic membranes. It must be added that definite histological changes occur in the capsule not infrequently, such as thickening and infiltration, and in severe cases hæmorrhages into its cavity. And Christian describes the appearance of hyaline droplets of varying size in the wall of the glomerular capillaries in uranium nephritis in rabbits.

As regards the connection between the functional change in the capsule and the morphological lesions in the tubules, nothing is known. It is generally accepted that nephritis in man is due to toxins carried to the kidney in the blood, and it may be induced experimentally in animals by the injection of toxins or of many irritant poisons, of which iodine, cantharidin, aloin, mercury, chromium, and uranium have been studied extensively. The primary lesion seems to be in the capsule, for albuminuria is often induced before the tubules undergo any obvious change. The cells of the convoluted tubules soon show the typical appearances of inflammation and degeneration, either from the poison acting on them in its passage downwards from the capsule, or probably from its penetrating the cells directly in the same way as the dyes in vital staining.

[1] The more recent literature is given by Baehr (1913) and Gaskell.

In general type the effects of all these poisons are similar, but some differences have been observed. Thus cantharidin causes marked albuminuria with apparently less injury to the tubules than the other poisons, at any rate in very acute poisoning; this may, however, arise from its more rapid action, for Eliaschoff describes marked destruction of the tubules after two to three hours. Suzuki has made a detailed examination of the histological changes under these poisons, and states that the lesions in the tubules are for the most part confined to the proximal convoluted tubule, some poisons acting predominantly on the upper of its segments and others on the lower; changes in the rest of the tubule arise from the casts carried down to them and not from the immediate action of the poisons.

The nephritis of phosphorus poisoning has been examined by Galeotti, who found fatty infiltration of the tubular epithelium and also some lesions of the glomerular apparatus.

In many instances the nephritic poisons first cause some diuresis without albuminuria, and in fact some of them, such as mercury and cantharidin, have enjoyed a reputation in therapeutics for this purpose. This may possibly arise from an early action on the capsule rendering it more permeable, or from dilation of the renal vessels. The increase in the urine is accompanied by a rise in the solids, including urea, phosphate, and chloride, though their percentage falls as in other forms of diuresis (320, 391). The blood-flow is rather faster than normal, while the oxygen consumption is lower and the venous blood issues redder than usual (Tribe, Hopkins, and Barcroft). The kidney in this early stage of poisoning is more susceptible to such diuretics as digitalis, theophylline and salines, which cause a greater increase in the secretion and a larger rise in the oncometer than are seen under them in normal animals (157).

This stage is followed in poisoning by one in which albumin appears in the urine and all the ordinary constituents fall in amount. The chloride may be reduced more than the others, probably because the animal eats little. Bardier and Frenkel (38, p. 749) induced unilateral nephritis by injecting chromate into the renal artery of one side, and then compared the urine secreted by the two kidneys; they found the quantity smaller and the total concentration lower on the injured side, but the chloride was higher at first, though it later returned to the normal percentage.

The acidity of the urine is often very high in nephritis, though the total titrated acid may not be above normal or may even be below it (Henderson and Palmer, 1916).

The effect of diuretics in this experimental nephritis has been examined repeatedly. Grünwald found theobromine increase the urine and cause the reappearance of chloride, which had been absent from salt-starvation, and concluded from this that in mercury poisoning the reabsorption in the tubules is not in abeyance. Boycott and Ryffel state that caffeine and salines cause less marked diuresis in uranium nephritis in rabbits and that the chloride rises less than usual during the diuresis; this last is the natural result of the smaller flow of urine, which permits of more absorption in the tubules. Urea also causes less diuresis and is more slowly eliminated than in normal animals; diuretics act more slowly than usual.

Hellin and Spiro also found that caffeine causes diuresis after aloin and chromate poisoning, but fails in cantharidin nephritis; they are therefore disposed to separate off cantharidin as a glomerular poison from the others, which they regard as acting on the tubules primarily; but it is not unlikely that the difference in reaction in their experiments was the result of a greater intensity of action by the cantharidin.

Phlorhizin continues to cause glycosuria and some diuresis in nephritis after these poisons, though in most cases the glycosuria is less than in normal animals (391, 324, 305, 163). But in cantharidin nephritis it is stated that no glycosuria occurs (Hellin and Spiro and Schlayer). In nephritis in man, phlorhizin causes less marked glycosuria than usual according to many clinical observers (391).

Strong salt solution is said to have much less diuretic effect in cantharidin nephritis than in the mercurial form (Galeotti).

Schlayer and his associates, Hedinger and Takayasu, have recently investigated the function of the kidney in various forms of experimental nephritis, and have made a notable, though not entirely successful, attempt to divest themselves of the morphological trammels. Besides describing the characters of the urine and the histological changes, in which they agree in essentials with previous writers, they recorded the renal volume by means of the oncometer, and examined the changes in it which followed stimulation of sensory nerves, the injection of adrenaline, diuretics

of the caffeine group, salines, and lactose. Theohari and Giurea, using similar methods, have confirmed Schlayer for the most part. Some obvious fallacies in the oncometer tracing from normal kidneys have been mentioned already (p. 122), but in nephritis a further point needs attention, for the inflamed kidney is distinctly swollen, and it is possible that its further enlargement may be limited by the firm inelastic capsule which surrounds the organ; and on the other hand, the contraction may conceivably be less obvious on the oncometer tracing, when the arteries contract. Conclusions as to the condition of the vessels drawn from oncometer tracings must therefore be accepted with the greatest reserve.

In nephritis from bichromate of potassium, mercury, and uranium, Schlayer found that in the early stages the oncometer showed the normal changes to his various reagents, and diuresis occurred as usual from salines and caffeine. In the later stages the increase in volume and the diuresis from these two were less, while the constriction after adrenaline and sensory nerve stimulation remained well marked. Finally caffeine and salt solution caused no dilation or diuresis, and the reflex and adrenaline constriction became distinctly less. In uranium poisoning a stage intervened in which salt solution caused a large increase in the oncometer volume, but this was accompanied by no diuresis, and in fact the scanty secretion still present was often arrested. Caffeine, however, caused a further dilation accompanied by secretion. Boycott and Ryffel failed to find any such stage, in which caffeine caused diuresis while saline failed to do so. In cantharidin nephritis Schlayer found all the reagents less powerful than in normal animals, and finally they failed to have any effect whatever either on the volume or the secretion of the kidney. Theohari and Giurea, however, found no such pronounced disability from cantharidin in dogs as Schlayer describes in rabbits, though the French observers also noted that the reactions were lowered to some extent; they state, however, that they obtained a larger diuresis from sulphate in these animals than in normal ones. In Schlayer's experiments with cantharidin, the blood pressure was low, and he recognizes this as a possible factor in the difference in reaction between cantharidin and the other poisons, though he does not appear to have given full weight to this consideration. This fall in pressure is still greater after the injection of arsenic,

which has not been shown to have any specific action on the kidney apart from its effects on the vessels of the general circulation (Suzuki).

Schlayer therefore classifies these poisons into two groups, "the vascular" comprising cantharidin and arsenic which act more strongly on the glomerulus, and "the tubular"—mercury, uranium, bichromate, aloin—which, he holds, affect the tubules chiefly. He admits that all of these act on both of these structures, and divides them only according to the point at which their action is more developed. Uranium nephritis is often accompanied by œdema and dropsy in rabbits, especially when they are supplied with abundant water and salt. In bichromate poisoning, œdema is less liable to occur, even though the renal lesion may be more severe than that under uranium. The nephritis is unquestionably a factor in the dropsy, but Heinecke and Meyerstein have shown that in addition the subcutaneous vessels are injured by the poison, and this important contributing cause is more marked under uranium than under bichromate.

Schlayer's work has attracted much attention, and several workers have attempted to confirm his results. Thus Pearce, Hill and Eisenbrey, repeating his experiments on the dog, obtain similar results in many points, but cannot accept his classification of the poisons into "vascular" and "tubular"; each type is met with, but small doses of cantharidin, a "vascular" poison, may cause the effects which are typical of the "tubular" group of Schlayer. In chronic poisoning with these last, anuria, accompanied by severe gastro-intestinal symptoms, occurred in some cases, while in others there was polyuria which passed into anuria under an anæsthetic. Suzuki also rejects the definite classification of Schlayer, and in particular criticizes the view that any of these poisons are pre-eminently vascular in action. MacNider points out that the polyuria under uranium arises from glucose being present in the urine, and also remarks that it is arrested by anæsthesia, which may cause absolute anuria, during which diuretics are of no avail though the volume of the kidney shows the usual changes under them. In other cases, the anæsthetic reduces the urine but does not actually arrest secretion, and in some of these diuretics act. He finds some symptoms from uranium which, according to Schlayer, imply vascular nephritis.

I have thought it well to go into Schlayer's work at some length, because it represents an attempt to penetrate more deeply into the pathology of nephritis than has hitherto been possible. The defects are largely due to the use of an unsuitable method of investigation, and to a failure fully to appreciate the grave injury caused to the capsule, as apart from the glomerular vessels, by the poisons employed. It is not yet established that these nephritic agents differ qualitatively in their action on the kidney so much as he supposes. Cantharidin and arsenic, it is true, often do not cause such grave lesions of the tubules as bichromates and mercury and their allies, but this is mainly due to the fact that the animals die much sooner, because the renal lesion is accompanied by marked effects in other organs, notably in the circulation. When the animal survives longer, the tubules are also involved, as was shown by Eliaschoff and many others. This extra-renal action of these poisons is recognized by Schlayer in the case of uranium, but its important bearing on the reaction of the kidney was not sufficiently appreciated in his consideration of cantharidin. Again, the changes in renal volume under saline diuresis and caffeine are now recognized to be of less importance than was formerly supposed, and many of his arguments are refuted by the consideration that diuresis may occur from each of these without any obvious vaso-dilation. These elaborate and laborious researches from the Tübingen laboratory appear to establish finally that the histological lesions in nephritis cannot be brought into direct relation at present with the functional behaviour, and that the invisible lesion of the capsule plays a much more important rôle than is often assigned to it. Schlayer and his pupils have investigated mainly the mechanical factor in diuresis in nephritis, and the importance of this factor is probably not so great as has been supposed. A more promising line of attack on the problem of nephritis would seem to be that offered by consideration of the chemical factors of diuresis (see p. 119); the extent of the renal lesion would be measured by considering how far it is able to meet variations in the composition of the plasma by altering the composition of the urine; quantitative estimations of the constituents of the plasma and of the urine would be the basis of the classification, and an extended preliminary study of the reactions of the normal kidney would be necessary.

A new nephritic poison has been discovered by Underhill, who found that sodium tartrate injected subcutaneously in rabbits and dogs causes destruction of the convoluted tubules of the kidney. Along with Wells and Goldschmidt, he has shown that the secretion of urine, and more especially of its nitrogenous constituents, is extraordinarily reduced; the injection of a mixture of urea and sodium chloride in these animals is followed by a considerable increase in the urine, and the chloride is eliminated adequately though more slowly than in normal animals, but the urea excretion is very deficient. The glomerulus, collecting tubules, and interstitial tissue are said to present no histological lesions, though detritus in the interior of the capsule is mentioned in some experiments, and the presence of albuminuria suggests that the Malpighian apparatus is not unaffected. The epithelium of the tubules is more or less completely necrosed, and as in other forms of nephritis, the convoluted tubules seem to be especially injured. The most striking feature is the complete absence of nitrogen from the urine which has been observed by Underhill in some experiments.

In this nephritis the destruction of the tubules was so striking, that its discoverer was disposed to regard it as a new form in which the lesion was confined to them, but further examination by Eisenbrey, Pearce, Underhill (1914) and their collaborators have shown that the glomerulus is also involved in the effects, although, as in the better-known forms of nephritis, the histological examination shows slight lesions here compared with those in the tubules.

Pohl (1911-12) has also described a new form of nephritis in animals poisoned with very small doses of uranium. The characteristic feature is a marked polyuria with little albumin in the urine, but large excretion of urea, total nitrogen, potassium, sodium, and chloride. The animals died finally of inanition, and the epithelium of the tubules was found necrosed or entirely stripped off, leaving the tunica propria exposed.

Circulatory Disturbance of the Kidney.

An interesting form of renal inefficiency is frequently seen clinically—that arising from cardiac failure. A special instance of this is offered in orthostatic albuminuria, in which the urine is normal as long as the patient remains in bed, but contains albumin when he rises; the cause of this is undoubtedly weakness of the circulation, in which the heart is directly affected, but the vasomotor function may be secondarily involved. During the albuminuria, the urine is less in amount and the threshold bodies are much reduced, while the non-threshold ones are less affected. Thus the water and chloride are greatly diminished, while the urea and total nitrogen, potassium, phosphate, and acidity fall less in absolute amount, and therefore often rise in percentage (223, 224, 398, 196, 264, 286). The effects of passive congestion of

the kidney have been examined experimentally by Rowntree, Fitz, and Geraghty by partial compression of the renal vein in dogs. They found the urine reduced in amount and containing albumin, casts, and some red blood cells. The excretion of lactose, salt and iodide, and phenolsulphonephthalein was slow and less perfect than in normal animals.

In these conditions the blood-flow through the kidney is altered in the opposite direction from that when the renal nerves are divided (see p. 100), and the urine is changed accordingly; in addition the deficient oxygen supply causes the capsule to become permeable by albumin. The lessened filtrate allows of more complete absorption, and the threshold bodies thus tend to decrease while the proportion of non-threshold substances rises.

Diabetes Insipidus.

Diabetes insipidus is a rare condition in which there is a marked and enduring polyuria without sugar and without any other apparent symptom from the kidney. The urine may amount to 12 or even 16-18 litres in twenty-four hours, and the loss of this amount of water entails thirst. The urine is clear, colourless, of low specific gravity (1002-1005 in severe cases), and of Δ as low as $-0{\cdot}15°$, while that of the blood is normal. The total amount of chloride, urea, phosphate, uric acid, and other constituents lies within the normal limits, but the percentage concentration is extremely low.

When chloride is given in excess in the food, its percentage in the urine generally increases, but does not reach that seen in normal conditions, and sometimes there is no rise in the concentration, the urine increasing remarkably in amount. This seems to be an exceptional response, however, for most cases respond to salt with a distinct rise in its percentage in the urine, even when the amount of urine also increases. Other substances, such as phosphate (Meyer) and urea (Forschbach and Weber), given by the mouth, appear in the urine in higher concentration, and may also increase that of the chlorides. The diuretics of the caffeine series sometimes fail to increase the urine while the concentration of chloride rises, but this is not invariably the case. The whole character of the urine resembles that seen under profuse water-drinking, and in fact there is great difficulty in distinguishing this

diabetes insipidus from the polydipsia which is occasionally seen in neuroses. Meyer points out that in diabetes insipidus the reduction of the amount of water taken leads to symptoms resembling the initial ones of uræmia, and attempts to differentiate it further from polydipsia by the fact that salt increases the amount of urine without a rise in the chloride percentage, but this test fails in most of the cases described as diabetes insipidus, including most of Meyer's own cases.

Meyer and Tallquist attribute the condition to the kidney being unable to concentrate the solids, but this is insufficient, for the urine is actually less concentrated than the plasma. And the kidney is capable of secreting a more concentrated urine when the constituents are supplied in the food in excess (Finkelnburg, Forschbach, Weber, and Lichtwitz), though the concentration does not reach the normal ; as a matter of fact enough salt cannot be swallowed for this purpose, for 100 grams of salt is needed to supply even 1 per cent NaCl in 10 litres of urine, and this quantity would entail alimentary disturbances.

The kidney has not been shown to be involved in the condition except secondarily in disposing of the excess of water; Meyer ascribes the symptoms to the effort of the kidney to eliminate the solids, which it can do only in a very dilute solution, but this view has not met with general acceptance. The excess of water taken may arise from the needs of other organs and tissues, which impose the sensation of thirst and thus involve polyuria. At present it is impossible to differentiate these conditions in which the polyuria is secondary from others in which it may perhaps be primary (Ebstein).

In most cases of diabetes insipidus, some disorder of the central nervous system is present, and though this has not been recognized in all, this may perhaps be due to the difficulty in diagnosis. There is therefore a general feeling that the symptom is of nervous origin, and many have attempted to bring it into relation with the puncture polyuria of Claude Bernard (p. 102). Against this interpretation it has been argued that in puncture polyuria the urine contains a high percentage of chloride, while the low concentration of chloride is one of the characteristics of diabetes insipidus. This argument does not deserve much attention however, for the high chloride concentration of the puncture urine is only seen in acute experiments, and it is almost certain that if the puncture

polyuria was more permanent the chloride would soon fall. At the same time the only argument in favour of a connection between diabetes insipidus and puncture polyuria consists in the fact that the urine is increased in each of them.

Another view has been suggested by Frank (1912), that the cause of the polyuria is a lesion involving the pituitary body. In a number of cases this has been shown to be the case, and on the other hand Schäfer has shown that injury of the pituitary in the dog leads to a marked and lasting polyuria. Thus in one experiment the average amount of urine per day was 110 c.c. before the operation, while afterwards it rose to 182 c.c. per day on the average, and was maintained at this height until the animal was killed three weeks later.

Tests of Renal Efficiency.

Impairment of the renal activity leads to the failure of the general tissues to eliminate their waste materials, and to general symptoms from the accumulation of these in the blood and fluids of the body. These are beyond the scope of this work, but I shall give a short sketch of such of the methods designed to diagnose early impairment as rest upon changes in the secretion.[1]

The first of these methods is intended to ascertain the total amount of solids excreted and their relation to the water. This may be done roughly by taking the specific gravity of the urine, which of course represents the relation of solids to fluid. What at first appeared an advance on this old clinical procedure, was the determination of the freezing-point of the urine [2] and its comparison with that of the plasma or serum, which may be taken as almost constant at $-0{\cdot}56^{\circ}$ C. The examination of the freezing-point—cryoscopy—of urine promised to become a familiar procedure a few years ago, but has fallen into disuse since its limitations were realized. The depression of the freezing-point below that of distilled water depends upon the total concentration of molecules and ions in the urine, and in ordinary conditions the chief of these are urea and the chlorides of the alkalies. Koranyi, who elaborated this method of examination, made use of

[1] Good reviews of this subject are given by Rowntree and Geraghty and their colleagues. See also Albarran.

[2] A résumé of the method and results is given by Hamburger, Osmotischer Druck und Ionenlehre, **2**, p. 247, Wiesbaden, 1904.

a fraction $\left(\frac{\Delta}{Cl}\right)$, in which the depression of the freezing-point was divided by the chloride content of the urine; he held that when this fraction varies beyond certain limits the kidney is acting abnormally. Claude and Balthazard gave more complicated formulæ, which have been interpreted by Steensma as merely measuring the impairment of the kidney by the diminution of the total solids of the urine, and the relative proportions of the nitrogenous constituents and the chlorides. These elaborate formulæ based on the determination of the freezing-point depression and on the estimation of chlorides thus give no more clue to the condition of the kidney than is afforded by the estimation of the chlorides and urea, or nitrogen, even if the latter is only approximate. The cryoscopic methods in fact only give a fallacious impression of accuracy which they do not possess, and may delude the physician into neglecting the more accurate but laborious methods of chemical analysis.

Another method of examination which is also of little value, is the determination of the electrical conductivity of the urine; this depends on the concentration of the ions in the urine, which generally varies with the alkali chlorides for the most part. It gives no definite information as to which salts are present, and as the salts vary in their way of excretion, the method cannot be said to do more than the estimation of chloride.

The estimation of the urea, or of the total nitrogen, of the urine has often been recommended as a test of renal adequacy, and at first sight seems the logical method. But the kidney may secrete a normal amount of nitrogen with very little urine, or, on the other hand, with a very high polyuria. Is each of these kidneys equally adequate to its task? And the amount of nitrogen excreted varies with the food, so that for any reliable examination both the intake and the output of nitrogen must be ascertained; but this involves accurate dieting and cannot be undertaken except in special conditions. Attempts have been made to evade this difficulty by comparing the concentration of the urea in the blood and in the urine in cases of suspected renal inefficiency, and Ambard has worked out a mathematical formula to express the relation between these in health, and considers that a departure from this formula indicates derangement of the excretion. But even if the correctness of Ambard's formula be

granted (and it has not been satisfactorily established), it is impossible to draw a number of samples of blood for urea estimations, and although Ambard satisfies himself with one sample, this is not sufficient to determine the daily variations, as he seems to consider.

The estimation of the residual (non-colloid) nitrogen of the plasma also fails to indicate the condition of the kidney, for part of this nitrogen is eliminated in the urine, but part (amino-acids) returns in the venous blood.

The difficulties involved in regulating the intake of nitrogen, chlorides, and other constituents of the urine are so formidable, that for ordinary conditions the results of the estimation of their output are of comparatively little value in the diagnosis of early renal inefficiency. It has, however, been suggested that light may be thrown on the state of the kidney by the readiness with which it eliminates an excess of any one of the constituents of the urine. For this purpose large doses of urea (10-20 grs.) may be given while the diet is kept fairly constant, and the time at which this excess is got rid of may be ascertained. More frequently salt has been employed as a test of efficiency, and Widal and Javal lay great importance on this test, and point out the important bearing the ingestion of salt has on renal dropsy and anasarca. In this connection it should be remembered that much of the chloride in the normal urine is not the sodium but the potassium salt, a fact which is not always realized in these researches. Albarran administers large quantities of water (500 c.c.) and compares the rates of excretion by the two kidneys by means of ureteral catheters. The test is of value in ascertaining disease of one kidney before surgical operation, but its results would be less certain in diagnosing impairment of both kidneys by nephritic changes.

Other methods of testing the efficiency of the kidney depend on the introduction of foreign substances which are excreted in the urine and which are easily distinguishable from the ordinary constituents. The chief of these have been iodide of sodium or potassium, lactose, and various dyes. Iodide appears in the urine in 15-30 minutes after it is swallowed and disappears from it in about 50-60 hours, except in traces. Lactose should all be excreted in about 6-7 hours, the urine no longer giving the test for sugar. Among the dyes, methylene blue, indigo-carmine, rosani-

line and phenolsulphonephthalein have been used chiefly, and of these the last seems to have the greatest advantages. It is injected intramuscularly in doses of 6 mgs., appears in the urine normally in a few minutes, and when the latter is rendered alkaline and examined by means of a colorimeter, 40-60 per cent of the dye is found to be eliminated in the first hour and 20-25 per cent more in the second hour (Rowntree and Geraghty). Renal inefficiency is indicated by a delay in the appearance of these substances, a slower rise of the excretion, and often by a prolongation of their appearance in the urine, the test being positive for many hours after the limit ascertained in normal individuals. For the most part these test substances all appear to respond in the same way to renal disorders, and the selection depends on their convenience and on their harmlessness. The rapidity with which the phenolsulphonephthalein gives results certainly offers great advantages in practice, and in addition the estimation is quantitative, while that of the others is merely qualitative, and thus unsatisfactory. Another test has been employed to a limited extent, the injection of small quantities of phlorhizin and the examination of the urine afterwards for sugar. In renal disorders sugar does not appear at all, or the reaction is given later than in normal conditions.

This functional testing has been criticized from several points of view. The reaction of the urine of course depends upon the rate of absorption of the drug from the point of application, and delay in absorption may thus simulate renal inadequacy. In practice, however, this does not seem to be a serious objection. Again, it has been objected that a kidney which proves inadequate in the excretion of one substance, may not be equally impaired in its reaction to others. But as a matter of observation, it appears that when one of these tests indicates renal inefficiency, the others as a general rule also suggest a similarly altered reaction. Supposed differences in the reaction to various tests have led Schlayer to divide nephritis into a number of sharply differentiated groups; but his claims have not been confirmed by other observers, and his classification is based to some extent upon altogether unproved assumptions as to the point at which the test substances are eliminated into the urine. The functional test is available as a means of ascertaining the efficiency of the kidney as a whole, but it cannot be employed at present to dis-

tinguish the different forms of nephritis, nor to determine what condition may prove to be present at the post-mortem examination. This is evident from the very different views held by different workers in this field, and also by the discrepancies between their clinical findings and the results of histological examination of the kidney (254, 81, 315, 264, etc.).

The method of functional testing seems to deserve more general attention than it has received hitherto. It has already proved of value in comparing the activity of the two kidneys in surgical cases, and it appears only to require further development to yield equally useful results in the various forms of nephritis which present so many difficulties in classification. But for this object to be achieved, it seems necessary to study the results in relation to the clinical changes and prognosis. Hitherto the observers have been obsessed with the desire to bring the results of their tests into accord with the histological appearances of the kidney, and as in nephritis the dominating anatomical feature is the condition of the tubules, the relation of the glomerulus to the elimination of the test substance has been neglected. It is true that lactose is credited with being excreted by the capsule (Schlayer), but all the others are assumed by most clinical workers to be secreted into the glomerular fluid by the epithelium of the convoluted tubules. Similarly, the phlorhizin test was introduced on the view that it measures the ability of the tubular epithelium to assume its new function of secreting sugar. It is possible that if all these tests were examined on the view that the foreign bodies are eliminated by the capsule, and that the impaired excretion in nephritis arises from the change in the filtration, which also accounts for the diminution in the ordinary constituents of the urine, the results of clinical examinations would be more compatible with each other. But if this is too much to expect, I would suggest that the clinical observers should accumulate a sufficient body of statistical evidence, averting their eyes meanwhile alike from the physiological laboratory and the post-mortem room.

The modern view holds that all these bodies are filtered through the capsule and fail to be reabsorbed by the tubules. Retarded excretion is due to the change in the capsule, which impairs filtration. No test has yet been suggested to detect alteration in the reabsorption, but there is at present no reason

to suppose that this function is often impaired in disease in man; one symptom which would at once draw attention to it, would be the appearance of sugar in the urine. The phlorhizin test succeeds in normal kidneys in arresting the reabsorption of sugar, while it may fail in disease because the small amount of the glomerular filtrate allows of the reabsorption of sugar even where the absorbing cells are impaired by phlorhizin; for it must be remembered that only a minimal amount of phlorhizin is injected. And the test is quite untrustworthy, because even in nephritis the cells may react to phlorhizin enough to cause some glycosuria.

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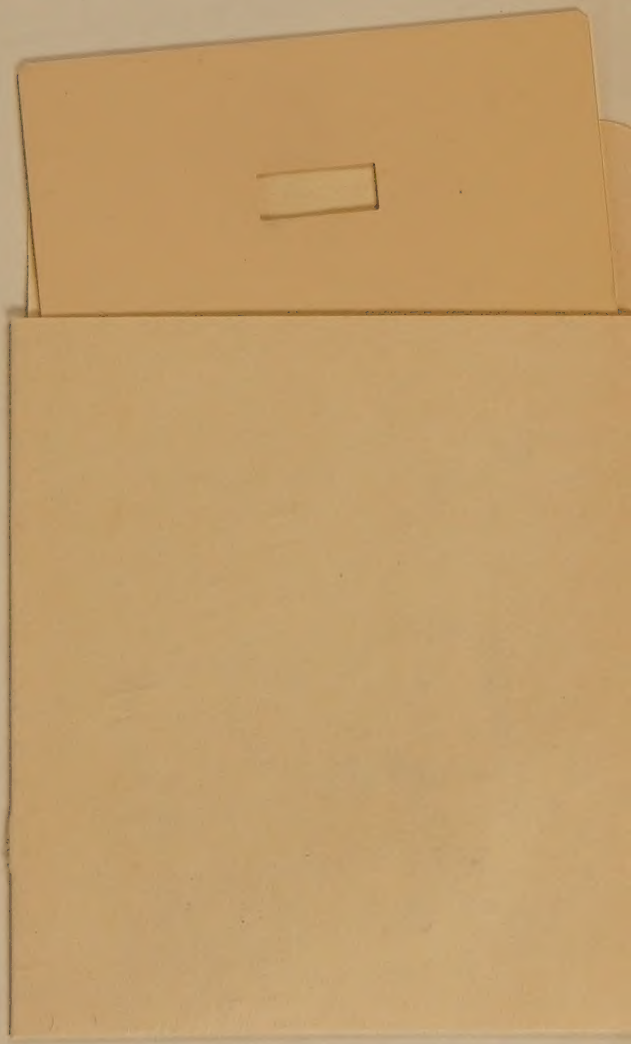

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